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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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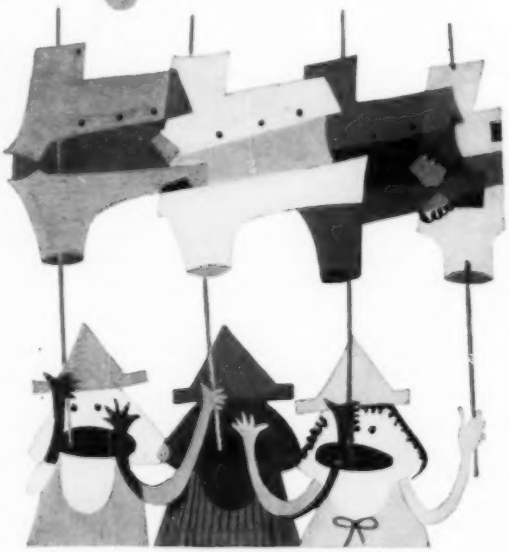

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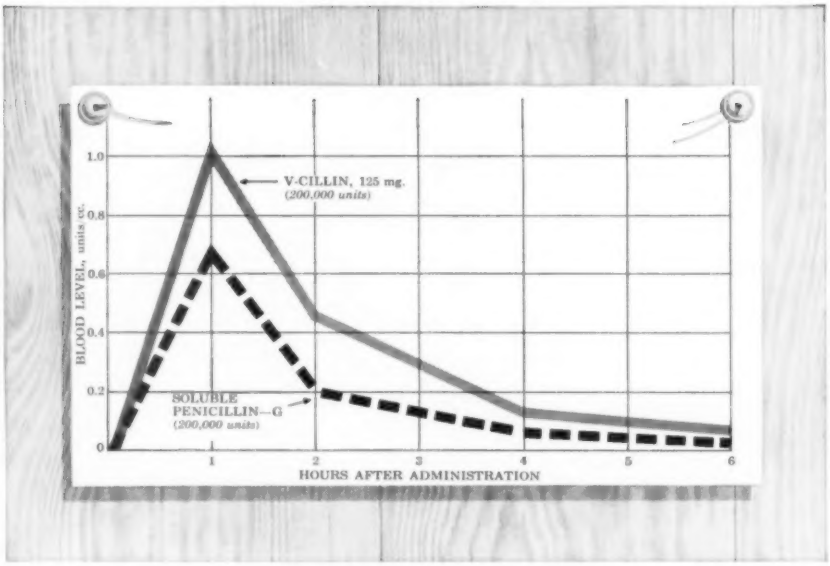

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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EXPERIMENTAL PROLONGATION OF THE LIFE SPAN*

CLIVE M. MCCAY, Ph.D., FRANK POPE
and WANDA LUNSFORD, A.B.

SEVEN hundred years ago the English scientist, Roger Bacon (1214-1292?), presented a logical guide for research regarding old age. He appreciated that man had a long span of life compared with most of his domestic animals. Since all animal life inevitably ages, man has a unique opportunity to study the phenomenon. Thus far man has made little progress in such research because human beings have chosen to expend their energies in improving the supposed comforts of living and methods of warfare.

At present man is not only making little use of animals for the study of aging, but he is neglecting important opportunities for controlled and non-injurious experiments upon man himself. In our own nation today, we have thousands of people confined in mental hospitals and other thousands serving life terms in prisons. It would be an easy matter to divide these into groups and study the effects of widely varied diets upon the diseases of old age, upon the deterioration of bones and teeth, and upon the failure in old age of hearing and vision. Such studies

* Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 10, 1955. From Cornell University, Ithaca, N. Y.

would introduce some interest in living to all segments of populations being studied. However, we are doing nothing because hospital administrators are too harassed with the daily problems of providing decent care without embarking upon time consuming ventures of begging for research funds, writing projects, attempting to guide individualistic researchers and publishing results. Possibly the dentists will be the first to make use of human beings for such research because dental projects are relatively simple to administer.[1]

A few examples of the many problems that could be attacked easily in institutions are the effect of long continued use of sugar upon old age, the level of calcium needed in the diet to maintain bones, the effects of different levels of fat in the diet, the relative merits of vegetarian versus omnivorous diets, the effect of sterols upon cardiovascular diseases, the effects of the long continued ingestion of alcohol, the effects of diets rich in milk, imbalances in nutrition between trace elements, vitamins, essential amino acids and unsaturated fats and the effects of various levels of dietary protein. At one time we were nearly embarked upon such a program when Dr. Fred MacCurdy was commissioner of mental hygiene but with the passing of the commissioner from the New York scene the vision was lost. Long before our time the biochemist, Otto Folin at Harvard, called attention to such neglected opportunities.

Today I am certain we do not know the real reasons for such well known phenomena as the longer life of women in comparison with men or the shorter mean span of life of physicians in comparison with other people. Both of these problems were discussed a century ago. Thus, one preacher asserted that women lived longer because they worried less than men. In the third edition of the text upon nutrition by James H. Bennet in 1882, the final chapter is devoted to the problem of the shorter span of life of physicians. Even at this date he rejected the common thesis that exposure to contagious diseases shortened the life span of physicians.

In considering research upon aging with animals, these two examples illustrate problems that can and cannot be attacked. It is evident that the problem of sex differences is subject to attack because white rats that die in old age at the end of their second year of life have the same sex differences as man. On the other hand it seems rather difficult to design experiments with rats that would give a conclusive answer to

the problem of the premature death of physicians. It is possible, however, to set up experiments with rats subject to stress, excess medication, poor diets, loss of sleep and excess alcohol to which some human beings are subject.

In considering any animal research one needs to keep in mind two or more basic concepts that have been debated regularly at most conferences concerning aging for many years. In the first place no conclusive answer has been given as to the possibility of aging without disease. Metchnikoff believed this was possible and cited examples such as the short life span of certain insects and what he thought was the natural death, like sleep, of a few older people. From our research of more than a quarter of a century we are convinced that when one lengthens the life span of an animal such as a white rat, he does so by retarding the onset of certain chronic terminal diseases.

In the second place, one finds in the literature a substantial number of articles indicating that the life span of an animal such as the white rat has been increased by feeding a high level of some substance such as vitamin A. Such research would seem to present studies of premature death from deficiencies or chronic toxicity of one group of animals in comparison with a well fed normal group. However, this depends upon one's point of view.

Before embarking upon a brief discussion of animal research, it may be worth mentioning two other fields that have been neglected in the study of nutrition. The first is the ability of animals to adapt themselves to diets that seem injurious in brief studies. Thus, the feeding of oxalate to young rats for a few weeks will waste body calcium but when the young rat is about half grown it overcomes this handicap so that the body utilizes calcium nearly as well in the presence of oxalate as it does in its absence. Hence, much of our worries over the eating of oxalate rich foods such as spinach or rhubarb seem unjustified.[2] Another example also concerns calcium assimilation in old age after long periods of consuming either high or low levels of calcium. It seems as if the body can adapt itself to low calcium levels in old age more effectively if the body has been used to diets low in calcium during the first two thirds of life.[3]

In the second place there is a slowly growing literature upon the vast numbers of new chemicals finding their way into foods and the imbalances that result from taking large amounts of a single substance

such as synthetic vitamins, or trace elements or amino acids. The literature in this field is little known because advertising it does not help to sell special chemicals, vitamins, trace elements or amino acids but there is great need for long time studies to determine the effect of imbalances upon health during the latter half of life.

Finally there is a naive lack of awareness on the part of some investigators using old animals to study gerontology, that such old animals are always suffering from several chronic diseases. Not long ago we gave investigators at Harvard two rare, thousand day old male rats for the study of an endocrinology problem. We prayed that they were aware that these rats probably had bronchiectasis, tumors and several other afflictions of old age.

Only a few years ago at a conference in New York City concerning the effect of the age of parents upon the number and quality of progeny, several investigators reported upon their researches using old mice. No one mentioned the chronic diseases of old age and every one seemed to assume that he was dealing with pure senility uncomplicated by special pathology. Even in the well established relation between mongolism in man and the age of the parents one wonders if chronic diseases may not be involved.

After this general introduction a bare outline will be given of some of our past experience that indicates that old age and the diseases that accompany it can be profoundly modified. After this we will conclude by presenting for the first time newer use of the old method of parabiosis for the study of aging in animals.

This whole discussion will begin and end, with a consideration of growth because the growth rate and attainment of maturity seem to have more effect upon the life span and the diseases of old age than any other variables.

For centuries the biological literature has contained occasional references to the virtues of fasting and slow growth in creating a long and healthy life. Fasting has been deeply involved in many religious practices. The virtues of a monotonous and limited diet have long been recognized in the prevention of overeating.

The first clean cut experiments proving that diseases could be modified profoundly were those of Moreschi[4] in Ehrlich's laboratory about fifty years ago. He found transplanted tumors could not grow in a partly fasted mouse.

For more than a quarter of a century we have studied retarded growth in various species of animals including rats, dogs, trout and insects. In all of these studies we have designed the diets to provide surplus amounts of all dietary essentials but never enough calories. Thus, each animal has had enough vitamins, inorganic elements, essential amino acids and fats but never enough calories for growth.[5]

The common white rat which passes through its normal span of life is very suitable for such studies because it is large enough for physiological studies and not very subject to parasitic diseases. Our poorest results have come from studies with dogs because fasted and retarded puppies are killed much more easily by parasitic diseases such as hookworms, than are normal animals. By the use of special sanitary procedures we have now improved our experimental techniques with dogs and hope soon to attempt again a study of retarded growth.

Rats retarded in growth by the above procedures and kept for the whole of life exhibit certain profound changes in their span of life and the diseases of old age. In the first place the span of life is lengthened substantially. Large numbers of rats can be produced that exceed a thousand days of age and some survive to 1400 days, or more than twice the mean span of life. Hence, man has it within his power to predetermine and lengthen the life span of one species of animals. Can this be true for all species?

In a normal group of rats, the females tend to live longer than the males. In retarded animals this is not true. They have equal spans of life. The growth retardation makes the male equal to the female in its long span of life. Possibly a study of this phenomenon will unravel the mystery of the longer survival of the human female.

In the second place our own studies and those of others have confirmed the early observations of Moreschi that the development of tumors is influenced profoundly by the retardation of growth. Normally about 12 per cent of our rats are afflicted with tumors of spontaneous origin at the time of death in old age. These retarded rats that survive much longer and usually die suddenly from lung diseases develop few tumors.

In the third place these retarded rats have certain parts of their bodies that seem to age at the normal rate and other organ systems that age more slowly. The bones seem to age at a normal rate and become very fragile in animals that are retarded and survive to 1400 days. The

eyes seem to fail at about the same rate but the individual variability is so great that it is difficult to measure. In contrast the hair of a retarded rat resembles the fine fur of a young animal. The skin of a retarded animal appears like that of a young one but when one cuts it one finds the tough characteristics of age.

A few problems concerning retarded growth have been given attention in our laboratory for many years but have never yielded conclusive results. A number of attempts have been made to determine if the learning ability or emotional stability of the retarded rat is superior to the normal. Most results have been inconclusive if the testing technique did not involve some reflection of a handicap from a chronic disease. In other words it seems that the brain of a normal old rat retains its functioning ability better than the lungs or reproductive organs.

In a recent unpublished report by a graduate student in psychology, Robert Ader, he concluded: "Although there were no significant differences in the behavior pattern observed, the direction of the differences was consistent, implying greater emotionality of the control animals." He concluded that possibly "the lower level of activity of the more emotional control group was more conducive to the avoidance of errors than was the agitated activity of the retarded group." This seems to say about what we often read in comparisons of the running of machines by seventeen and seventy year old workers, namely that the older worker moves more slowly but achieves the same amount, due to the exactness that comes from experience.

One inherent difficulty in psychological testing of retarded animals is that one cannot use motivation from hunger unless he feeds his retarded animals and permits growth. In this field we would like to test the loss of ability to select essential nutrients in relation to age since we found some years ago that the ability to select such essentials is very marked when rats are young but this ability gradually declines with age.[6] However, we have found no satisfactory method of testing retarded rats that are always hungry.

The problem of loss of reproductive powers in both normal and retarded rats has been studied from time to time. In one test some years ago in which males were fed marginal allowances of vitamin E, it was found that these male rats lost their fertility early in life but that this had no effect upon the total span of life. Retarded male rats seem to be permanently sterilized.

Some of the females, however, can be bred after a substantial period of retardation but none have exceeded the normals. In our rat colony the age record for reproduction by a female rat has been 26 months, while the oldest retarded rat that could produce a litter was 17 months. For some years we have been selecting rats from litters born very late in the life of females to determine if this might lead to a strain of rats that could normally attain a greater life span. No results have come from this study thus far.

Another problem of retarded growth concerns the ability of retarded rats to prevent the development of bone tumors. Some years ago we found that the feeding of 5-6 microcuries of calcium 45 per gram of body weight to young rats for a two week period shortly after weaning led to the production of bone tumors in the adult rats starting at about 200 to 300 days of age. All rats given this level developed bone tumors. Below this level a bone tumor is rare.[7]

One can then ask if the retardation of growth in such rats might prevent the development of tumors of bones as it does in soft tissues or if the retardation of growth might prolong the span of life and hence make the bone tumors appear at a much later age from lower levels of Ca45. This experiment was started in the summer of 1955 but has given no results thus far.

In this latest study both hamsters and rats are being used since we know of no retarded growth nor tumor studies of this type with hamsters. The use of several species seems important from our experiences with dogs.[8] Using the same regime of feeding calcium 45 and the same dosage in relation to body weight, we have produced no bone tumors within the first year of life. The Ca45 merely produced thinning of the shafts of the long bones so that some were fractured spontaneously as shown in x-rays. These healed without splinting and these female beagles seem quite normal today in their second year of life.

Hence, there may be marked species differences in the response to changes initiated by radioactive materials when fed to young rapidly growing animals such as rats, dogs, hamsters and other species. Although the margin is wide between the level of radioactive calcium used as a tracer and the level that produces bone tumors, the species variation may be important especially since some Ca45 is being fed to human beings in some laboratories.

Both the hamster and the dog may deserve more extensive use in

research upon aging since the hamster seems to be subject to forms of arthritis in old age similar to those of man and since the dog seems subject to changes in old age similar to those of man such as alterations in the prostate.[9]

Inasmuch as retarded animals never attain normal adult size, but are always somewhat stunted, one may ask if the smaller animal is destined for a longer span of life. This has interest as a human problem since our culture tends to accelerate the growth of children and produce larger adults. In studies of normal rats that have grown as rapidly as possible we have attempted to determine if there is a relationship between ultimate body size and total length of life. Contrary to what one might believe there is a very positive correlation between size of body attained and length of life. We are not aware of similar studies with human beings but they may exist.

Next in importance to retardation of growth as a means of lengthening the span of life of experimental animals is the technique of keeping animals from becoming fat. The life span of rats is lengthened if they are kept thin either by restriction of food intake or by exercise. Even if the rat is allowed to be overweight until middle life and then obliged to reduce, there is a favorable influence upon length of life.

In studies of aging one is faced with the basic problem of whether it is possible to improve health without any lengthening of the span of life. In other words, can one modify a given organ system without change in that one which terminates life in old age. As a concrete illustration one may ask if one can improve the quality of bones in old age without modifying the bronchiectasis that ultimately destroys the animal.

A number of studies with white rats has indicated that one can feed diets of special composition such as liquid milk with the result that the bones remain denser in old age and the teeth show no decay. However, chronic bronchiectasis and other afflictions of later life proceed at their usual rate. Hence, the rat dies after the common mean span of life but has superior bones and teeth at the time of death.[10]

In concluding this discussion a brief review will be given of our experiences during the past three years in exploratory research to determine if the methods of parabiosis may have some use in fundamental studies of aging. In his review of parabiosis, Finerty[11] states that this joining of two rats by surgical operation was first used in Claude Ber-

nard's laboratory by Paul Bert in the 1860's. Through the common capillary circulation the two rats share many but not all of the constituents of the blood.

Our own interests in parabiosis arose in the course of studies upon the decay of teeth. Kamrin[12] made use of parabiosis by feeding one of each pair of rats a given carbohydrate, to learn more about the food factors responsible for decay. He also gave us our initial lessons in surgery for this study.

The first question to be answered was that of the age that could be attained by a pair of rats parabiosed shortly after weaning. Only two pairs were prepared. The older of the two was killed when 527 days of age because one developed a chronic bladder infection and we felt that evidence was adequate for such survival. Such survival is equivalent to 53 years in the case of man.

Only one study of interest was made upon these old parabiosed rats during the latter half of their lives. While these rats were alive, a bacteriologist from Queen Elizabeth College in London, Dr. Rachel White, was making comparative studies of the microorganisms of old and young rats in our laboratory. She had found the greatest contrast in the number of yeasts in the feces of old and young rats fed similar diets. Several studies were made of these parabiosed rats with time intervals of several weeks between samplings. Every test showed consistent differences in the microflora and this difference was maintained. Thus, in spite of living united from an early age and eating from a common food supply, the distribution of microorganisms in the intestinal tract was characteristic for each individual.

The next studies made during the past summer were designed to help secure answers to the classical problem of whether a young animal has substances circulating in its blood that can rejuvenate the old or vice versa, whether the blood of the old can produce aging in the young.

Nearly a century of research indicates that the basic problem of uniting a young and a middle aged or old animal, would probably be due to failure to effect unions due to skin sensitivity. In most parabiotic research, litter mates are used but much has been done in uniting non-litter mates allowing for about two thirds failures.

In the hope of reducing inherited allergies to a minimum and still have rats of quite diverse ages, a series of litters was produced using the same dam and sire. Since we have not learned to make parabiotic

unions between rats of very different sizes, the older rats were retarded in growth for as much as eight months before the operation was performed. Thus, we had available rats of quite different ages, the same size and from the same parents.

Parabiotic unions were made between such rats in July and they are still in good condition now in October. In such unions it looks as if the most important factor is the anesthesia. The reactions of rats of the same size but different ages to the barbiturates seem quite different. In the next place the temperament of the two animals seems important. If two rats are not adjusted to each other, one will chew the head of the other until it is destroyed.

In some cases one meets the problem of "parabiotic toxicity" which has long been recognized by workers in this field. Under such conditions both rats may eat and drink normally but one seems to be drained of certain essentials. The rat that suffers from this drainage shows ears and tail that are pale and blanched while the other has these organs that are very red. During the past summer it has proved possible to take such rats apart and unite the successful one to a new partner.

By the careful use of sedatives over a long period of time it may be possible ultimately to unite rats of very different sizes and ages but this has not been tried thus far.

Since retarded rats age very rapidly after they attain maturity in comparison with normal rats, it may be possible to learn something about the relation of the internal milieu to aging by this method of study. We may even find it possible to test the hypothesis of J. H. Cohausen in his book of 1744 entitled "Hermippus redivivus," in which he is said to have advocated that an old man regains some youth by acquiring a young woman.

Summary

Studies covering a period of a quarter of a century indicate that the life span of experimental animals such as the white rat can be increased much by the retardation of growth. Under normal conditions the female outlives the male but when the life span is extended there are no differences. Chronic terminal diseases such as tumors are much restricted by retardation of growth. Under normal conditions animals that attain a larger body size have longer spans of life. Early sterility of either sex does not influence the total span of life. Under normal

conditions animals that grow larger tend to have longer spans of life. By certain feeding regimes such as the use of large amounts of fresh milk, the bones and teeth may be better preserved in old age but the span of life is not lengthened because the terminal disease involves the lungs which are not affected by the feeding regimes.

The old technique of Paul Bert of parabiotic union by which pairs of rats are sutured together so that they have a common capillary circulation may have use in the study of aging. By combining the techniques of retarded growth and the production of successive litters from the same parents, it has proved possible to effect parabiotic unions between rats that are 60 and 300 days old. The two most important factors in such operative procedures seem to be the proper dosage of anesthetics for the rats of different ages and the temperaments of the two animals. Maladjusted animals destroy each other. In case of failure one parabiotic rat can be severed from the union and combined with a new mate.

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ARTHRITIS IN THE ELDERLY PATIENT (OSTEOARTHRITIS)*

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DR. T. W. TODD[1] wrote: "To the popular mind the aging of Man is expressed in skin and hair, and nails and teeth, in bones and muscles, in the body that has to perform the command of the will. But whereas the aging in skin and teeth, in hair and nails may take place without necessarily affecting the body as a whole, aging in the muscles and bones bites into Man's pride and gives him a sense of the passage of time which he fain would conceal even from himself. Conscious of the waning strength and endurance, he seeks for substitutes, accepting with difficulty the limitations imposed by Time and inferring therefrom a suggestion of infirmity."

Osteoarthritis, otherwise referred to as degenerative joint disease, hypertrophic or senescent arthritis, is a structural disease of joints which may develop spontaneously with advancing age (primary osteoarthritis) or at any period of life as a sequel to mechanical injury, deformity, infection, or any other condition that leads to degeneration of articular, hyaline cartilage (secondary osteoarthritis). A combination of two factors is involved in the pathogenesis of osteoarthritis. The primary factor leads to degradation of articular cartilage and the secondary one usually consists of superimposed mechanical or functional stress (such as weight bearing or excessive motion) or prolonged nutritional deficiency of the cartilage. In the spontaneous type of osteoarthritis, the primary factor is believed to consist of senescent changes in the cartilage. Whereas this aging of cartilage may occur as a generalized process, osteoarthritis develops in but few of the joints, depending, as a rule, on the mechanical conditions present locally. The exception to this rule is the very familiar arthropathy of the distal interphalangeal joints characterized by Heberden's nodes. Why these joints which are singularly free

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from stress or strain or excessive motion should be so commonly affected remains a mystery.

Incidence: Degenerative joint disease is the most common type of chronic arthritis. Although it affects an older age group and is not so frequently or severely disabling as rheumatoid arthritis, it, nevertheless, is of considerable economic importance. In an industrial population in New York City consisting of 23,881 persons, of whom 89 per cent were males, and the average age 45 years, it was found that degenerative joint disease was the second most common musculoskeletal disorder, being exceeded only by bursitis. Of all patients who presented objective evidence of musculoskeletal disease, degenerative joint disease (osteoarthritis) was diagnosed in 14 per cent. It occurred more frequently than gout and rheumatoid arthritis combined. The site of involvement which gave rise to symptoms was in order of descending frequency, spine 73 per cent, knees 25 per cent, hips 7 per cent and other joints 5 per cent. Symptomatic degenerative joint disease occurred in 12 per thousand employees during the year 1954.[2]

History: It is now common knowledge that osteoarthritis is among the oldest diseases in history. It is known to have afflicted prehistoric animals and Neanderthal Man (40,000 B.C.). Although Hippocrates observed that joint disease was common in the aged, a distinction between osteoarthritis and the other types of arthritis was not made until Weichselbaum[3] in 1872 accurately described the gross and microscopic changes that characterize this disease. In 1890 Sir A. E. Garrod[4] introduced the term osteoarthritis. Nichols and Richardson[5] later (1909) correctly described the characteristic pathological changes and emphasized the distinction between osteoarthritis and rheumatoid arthritis. It is interesting to note in passing that more than a century previously, Heberden[6] in 1803 had pointed out that the osteoarthritic digital nodes, which now perpetuate his name, had "no connection with gout." In 1941 the New York Rheumatism Association recommended that the term degenerative joint disease be officially used for this disease[7] and it was later adopted by the American Rheumatism Association.

Despite the ancient history of this disease, quite important contributions to our knowledge have been made within the last two decades. A better understanding of the pathogenesis of osteoarthritis in general,[8] and the knee joint,[9] hip joint,[10] and Heberden's nodes[11] in particular has been gained from critical review of past concepts, meticulous an-

alyses and sound interpretations of the characteristic gross and microscopic findings, in conjunction with application of new disciplines and technical methods, including experimental pathology, histochemistry, and angiography.

Sequence of Pathological Events: The first step in the chain of pathological events is degeneration of articular cartilage. When studied under the electron microscope, aging hyaline cartilage reveals changes in the cartilage cells, collagen fibers and interfibrillar ground substance.[12] The cells show degenerative changes containing coarse cytoplasmic granules. Calcium and fat granules appear on the fibers at the margin of the cell capsules. The architectural pattern of the collagen fibers has changed from a uniform network of fine fibers to an irregular mesh of coarse, curved fibers that retain their cross striations. The matrix loses water, becomes hardened, less elastic, less permeable and later disappears, exposing the collagen fibers. Chemical analysis of cartilage that has undergone fibrillation discloses an alteration in the ratio of collagen to chondroitin sulphate.[13] The former constitutes the fibrillar framework of the cartilage and the latter is the mucopolysaccharide of the ground substance in which the fibrils are embedded. The cartilage loses its elasticity and resilience, and its surface layers become flaked, ulcerated and denuded. Clefts and fissures appear perpendicular to the articular surface and attribute to the cartilage a felt-like filamentous appearance. As attrition advances, erosion and loss of cartilaginous substance follow. The initial stages of senescence and degeneration transpire imperceptibly; clinical symptoms do not appear until the stage of cartilage fibrillation, disintegration, and destruction is reached.

The secondary changes that follow in response to cartilage injury are productive or hypertrophic in nature. Unfortunately, the response is often vigorous and exuberant and results in further impairment of articular function. Every structure of the joint often participates in this reaction; the calcified cartilage which is at the base of the articular cartilage, the subchondral bone, synovial lining, periosteum, and capsule.

In the area where articular cartilage has been reduced in depth, the calcified cartilage becomes thicker, denser, and reduplicated. In the subchondral bone, blood vessels, fibroblasts, and endosteal cells proliferate. This vascular granulation tissue breaks through the calcified cartilage and also advances to the surface, replacing disintegrated articular cartilage. Thus, as new bone is formed and later thickened, the

articular surface which had been denuded of its cartilaginous lining is reinforced with a stout subchondral plate of bone (eburnation).

As destruction of cartilage becomes advanced and as blood vessels extend into these areas osteophytes appear, first, at the lateral margins of the joints where the synovialis merges with the articular cartilage and also where the capsule and periosteum meet. These are proliferating, bony excrescences, usually cancellous, whose marrow spaces are continuous with epiphyseal marrow. They are covered with either fibrocartilage or periosteum, never with hyaline cartilage. It is held by some investigators[10] that osteophyte formation is not limited to the marginal zones, at the junction of synovia with cartilage or periosteum, but may also occur in any area of the joint which does not transmit weight. The two prerequisites for osteophyte production appear to be destruction of cartilage and low, rather than increased, articular stress.

Changes in the synovial lining do not appear until relatively late. In striking contrast to that seen in rheumatoid arthritis, the synovial membrane is fibrotic, not inflamed or hyperemic, and only slightly and inconstantly proliferative. When fragments of disintegrated cartilage or bone are dislodged and fall to the synovial surface of the joint, phagocytosis by the lining cells occurs and hyperplasia develops.[14] This event is followed by considerable fibrous thickening and shrinkage of the joint capsule. Tightening of the capsule may contribute to the limitation of joint motion and, since the capsule is supplied with somatic and autonomic fibers, it will give rise to pain and reflex muscle spasm when stretched beyond its restricted limits.

In the pathogenesis of osteoarthritis, the productive phase just described—which includes reduplication and thickening of the calcified lamella, eburnation of subchondral bone, proliferation of osteophytes and fibrosis of capsule—occupies an intermediate position between the initial phase of cartilage degeneration and the final period of osseous destruction. As a result of ischemic changes that occur in the advanced stages, small areas of aseptic necrosis of bone develop. Probably unrelated causally to this process is the appearance of multiple bone cysts. It has recently been suggested that these cysts do not result from bone destruction since they are lined by sclerotic trabeculae and not degenerating bone. When carefully dissected, all cysts are found to communicate with the joint space by stomata. In the cysts, which range in size from 1 mm. to 2.5 cm., are present poorly vascularized fibrous

tissue, fragments of articular cartilage, and synovial fluid. Landells[15] hypothesized that the cysts arise from intrusion of the synovial fluid under pressure into subchondral bone at the site of cartilage degeneration.

The many changes which occur in the evolution of osteoarthritis—degenerative, productive, and destructive—together with the inevitable redistribution of forces acting through the joint, lead to alteration in the structure, shape, and not uncommonly to displacement of the articulating ends of the affected bone. Thus, in osteoarthritis of the hip joint, the head of the femur is characteristically flattened and extruded laterally (Fig. 5).

Factors that Contribute to Development of Osteoarthritis: Injury to cartilage is the critical factor that initiates a chain of pathological events that leads inexorably to osteoarthritis. In cases of secondary osteoarthritis, the cause of this injury is known, such as fracture, deformity, avascular necrosis, infection, neurotrophic arthropathy, gout, osteochondritis, etc. In primary or spontaneous degenerative joint disease, however, the etiology remains obscure. Undoubtedly advancing age is intimately related to the development of this disease since the articular cartilages suffer involutionary changes with aging. In 1,002 autopsies, Heine [16] determined the incidence of cartilage degeneration and of osteoarthritis in relation to the advancing decades of life. In the knee, for example, 3 per cent of subjects in the second decade exhibited cartilage changes. The incidences in each successive decade increased as follows: 9 per cent, 48 per cent, 74 per cent, 87 per cent, 92 per cent, 97 per cent and in the 9th decade it was 100 per cent. Structural evidence of osteoarthritis in this joint occurred less frequently but was again related to age; none below age 30, 1 per cent in the 4th and 5th decades and 2 per cent in the 6th decennium. From then on the incidence rose in each succeeding decade to 12, 33, and 39 per cent. Bennett, Waine, and Bauer[9] in an outstanding study on the structural changes in the knee joints of 63 persons at various ages who had presented no symptoms of joint disease reported similar findings. (Fig. 1). But senescence could not be considered the direct cause of primary osteoarthritis since this disease is not restricted to the elderly, having been encountered during the second decade; nor is there a direct relationship between age of the subject and severity of cartilage degeneration.[10]

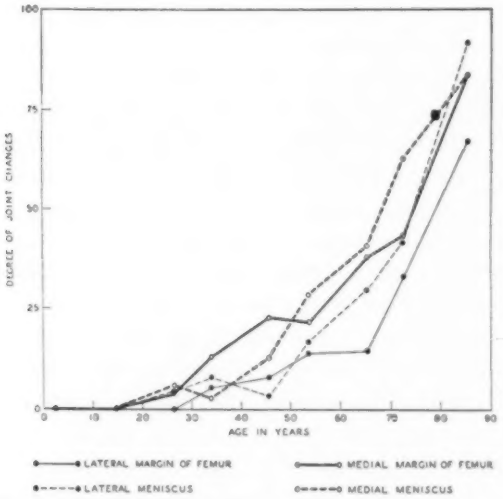

Fig. 1—Average degenerative and proliferative changes in the perichondrial margins of the femur and in the menisci at each age decade. (From Bennett, Waine and Bauer, ref. 9. Reprinted by permission of The Commonwealth Fund.)

Anatomically the distribution of degenerative joint disease is approximately equal in both sexes with the exception of terminal finger joints (Heberden's nodes) which are affected 10 times more frequently in women than in men.[17] Clinically, symptoms of osteoarthritis apparently occur more frequently in women than men.[18]

As has been mentioned, mechanical factors, like weight bearing or excessive motion, such as occur in the hip and knee or acromio-clavicular joints, contribute to the development of osteoarthritis. An important additional factor has unexpectedly and recently come to light. Trueta and associates[10] studying osteoarthritis of the hip joint with elegant techniques and unusual thoroughness concluded that the commonest sites of osteoarthritis are those sections of the femoral head and acetabulum which undergo no pressure and conversely, the areas which sustain joint pressure and carry most weight, overlying a reinforced system of bone trabeculae, survive longest in a relatively normal state. By pressure areas are meant those parts of the femoral head and acetabulum which participate in active joint functions and hence undergo

intermittent compression of movement and weight bearing. This allows, it is believed, adequate tissue-fluid exchange in the cartilage and thus promotes normal metabolism.

The role of heredity as a contributory factor to degenerative joint disease of the terminal finger joints and to a lesser degree of the hips, has been carefully assessed by Stecher.[17] It was concluded that idiopathic Heberden's nodes are inherited as a sex-influenced characteristic which is dominant in women, recessive in men, and depends upon a single autosomal gene. Accordingly, an affected woman would transmit the disease to one-half her daughters. One-half her sons would inherit the trait and would transmit it to one-half of their children although they themselves would not manifest the disease. Because Heberden's nodes are recessive in men, a man would develop them only if he inherited them from both parents. Stecher believed there was a definite association between the development of Heberden's nodes and the menopause, although in individual patients the nodes appeared at times ranging from 20 years before to 15 years after the menopause. In osteoarthritis of the hip joint, the genetic relationship is much more difficult to establish. Osteoarthritis will develop in hips that are deformed as a result of hereditary or familial disorders such as Legg-Calve-Perthes disease or congenital dysplasia of the hip. Early correction of these deformities may prevent the development of degenerative joint disease.

A number of clinical observers have recorded the impression that degenerative joint disease may be related to thyroid deficiency and others noted an association with obesity. Erdheim[19] described a type of peripheral and spinal joint disease seen in acromegaly. In view of these clinical inferences, it is of special interest to note the experimental findings of Martin and Ruth Silberberg[20] who have studied the effects of anterior pituitary hormone, fat diet, and thyroid hormone on rate of growth of articular cartilage and on spontaneous osteoarthritis in guinea pigs and mice. They found that injections of anterior pituitary, or transplants of this gland, caused intensified growth of the articular cartilage and regressive changes of cells and ground substance leading to severe degenerative joint disease. In mice fed a high fat diet, the incidence of osteoarthritis was increased two-fold and the onset of the disease significantly accelerated.[21] However, body weight per se or obesity did not appear to be an important factor in initiating articular changes. It is noteworthy that a number of animals remained free of

osteoarthritis even in old age and when fed a fat-enriched diet. The effect of such a diet on the development of joint disease was conditioned by the functional state of the thyroid. In strains of mice with inactive thyroids there was a high susceptibility to spontaneous osteoarthritis and a marked intensification of the joint disease when a high fat diet was given, whereas in mice with active thyroids, the susceptibility was low and the effect of diet only slight. The Silberbergs[22] concluded that thyroid hormone plays a major role in the maintenance of adult articular structures (in mice) under normal and abnormal conditions. Whether these provocative observations on small laboratory animals apply to man remains to be determined. Such investigations on human osteoarthritis might prove to be quite rewarding.

Clinical Features and Diagnosis: The two most common types of chronic joint disease that are encountered in middle-aged and elderly patients are osteoarthritis and rheumatoid arthritis. No one today will question that these diseases are separate and distinct nor that they can be readily distinguished from each other. It is therefore surprising to find that they are frequently confused. Since medical care is so widely divergent in both conditions, it is of considerable practical importance that a correct diagnosis be made. The basic difference between the two types of arthritis is that rheumatoid arthritis is an inflammatory and osteoarthritis a degenerative disease. There are no constitutional signs of "infection" in cases of osteoarthritis such as fever, weight loss, weakness, fatigue, generalized muscle wasting, anorexia, perspiration, anemia, leukocytosis, hyperglobulinemia and elevated sedimentation rate. In osteoarthritis of the peripheral articulations, the affected joints are painful, stiff—especially after being kept in a fixed position for a prolonged period—and somewhat tender. But they are bony, hard, irregular, or knobby upon palpation. They are not warm or pink, and soft periarticular swelling is lacking. Subcutaneous nodules are never associated with osteoarthritis and the sheep cell agglutination test is negative. The typical patient with osteoarthritis will, with the slightest encouragement, boast of aggressive good health for a person his age, save for a few stiff joints. The average patient with rheumatoid arthritis is much less sanguine and more insecure.

A common misleading feature in the differential diagnosis is the presence of swelling of the proximal interphalangeal joint. It should be remembered that one-fourth of the patients with degenerative joint

disease who have Heberden's nodes also have involvement of the proximal finger joint.[11] In this disease the joint is bony, hard, and irregular, and the metacarpophalangeal joints are remarkably unaffected. X-rays of the hands show osteophytes, eburnation and absence of osteoporosis at the phalanges; with rare exception, the heads of the metacarpal bones and the contiguous joints are well preserved (Fig. 2).

In osteoarthritis of the intervertebral articulations of the spine, hypertrophic bone changes may cause narrowing of the foramina with resulting irritation and compression of nerve roots. The symptoms will of course vary with the spinal segments involved. Collins[8] made a useful and clinically important distinction between osteoarthritis and osteophytosis of the spine. The term osteoarthritis is limited to synovial-lined, diarthrodial joints; hence such a diagnosis is restricted to degenerative disease of the interfacetal or apophyseal articulations. The term osteophytosis is used to describe the formation of spurs on the margins of the vertebral bodies which are so commonly seen in x-rays of the spine of middle-aged people (Fig. 3). These osteophytes rarely give rise to symptoms although they are too often indicted.

In Figures 4 and 5 are illustrated typical x-ray changes seen in osteoarthritis of the knee and hip.

Treatment: The one remedy most frequently effective is the simple assurance by the physician that the patient does not have rheumatoid arthritis and consequently is not threatened with invalidism or crippling deformity of multiple joints. Since medical treatment is always palliative and disability from this disease rarely severe, there generally is little justification for the use of drugs that are potentially hazardous such as steroids (systemic administration), corticotropin, or phenylbutazone, or for drugs that are of no proved value such as colchicine, cinchophen, iodides, snake venom, liver extracts, vaccines, or antibiotics. Hormonal therapy such as thyroid, estrogens and androgens should be administered only when there is evidence of a specific deficiency. Rest for the affected joints, physical therapy, corrective exercises, and aspirin are beneficial. Obesity should be corrected, and a sustained and earnest effort at weight reduction should be made. Repeated intra-articular injections of 25 mg. of tertiary-butylacetate or the acetate of hydrocortisone is often quite helpful in tiding the patient over a troublesome period.

Corrective surgical measures are considered in but a small percentage

Fig. 2—Photograph of x-ray of left hand of 63 year old white female illustrating typical changes associated with osteoarthritis of terminal finger joints (Heberden's nodes). The joint spaces are narrowed, irregular and uneven, and the joint surfaces widened. The subchondral bone is of increased density (eburnation). Multiple small cysts are present in the distal ends (subchondral bone) of the middle phalanges. An osteophyte appears at base of terminal phalanx of thumb. The metacarpophalangeal joints are unaffected.

Fig. 3—Photograph of x-ray of cervical spine (lateral view) of 74 year old white female, illustrating osteophytosis at the inferior border of the sixth and superior border of the seventh cervical vertebra (both anteriorly and posteriorly). The intervertebral space is narrowed as a result of disc degeneration. Eburnation is seen at the opposing surfaces of the affected vertebral bodies.

Fig. 4—Photograph of x-ray of knee (lateral view) of 70 year old white female. Spurs extend from anterior, posterior and inferior surfaces of the patella. As a result of destruction of the articular cartilages, the retropatellar space and the space between the femoral condyles and tibia are narrowed. A large ossified loose body appears posterior to the femoral condyles.

Fig. 5—Photograph of x-ray of hip of white male, age 62, illustrating typical changes associated with osteoarthritis of the hip joint. Destruction of cartilage and bone is seen (malum coxae senilis). The joint space is markedly uneven, narrowed in the superior aspect and widened in the inferior portion. The head of the femur is characteristically flattened. There is increased density (eburnation) of the subchondral bone of the acetabulum and femoral head. Overgrowth of bone at the inferior margin of the femoral head is present. Multiple cysts appear in the juxta-articular bone on both sides of the joint.

of advanced cases of knee or hip involvement associated with insufferable pain or serious disability. A variety of surgical procedures has been recommended. These include fusion of the joint (arthrodesis), arthroplasty, debridements, neurectomy, synovectomy, and patellectomies. The literature on these measures is both abundant and controversial. The subject is too complex to be adequately discussed in this paper, even if the author were competent to do so.

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ANOREXIA NERVOSA*

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THE purpose of this paper is to review some of the literature on the subject of anorexia nervosa and to present in brief the salient factors of ten case histories of patients who have been treated at the New York Hospital-Westchester Division over a period of fifteen years (1938-1953). There has been an increased interest in this condition paralleling the recent growth of interest in psychosomatic problems.

The clinical syndrome was given the name anorexia nervosa by Sir William Gull[1] in 1874. He observed that the disorder occurred in young girls, and described the anorexia, the extreme emaciation, amenorrhea, and the restless activity. He differentiated the disease from what was thought by some to be a form of tuberculosis by the absence of any manifestations of infection. He stated: "The want of appetite is, I believe, due to a morbid mental state. I have not observed in these cases any gastric disorder to which the want of appetite could be referred. I believe, therefore, that its origin is central and not peripheral. That mental states may destroy appetite is notorious. The treatment required is obviously that which is fitted for persons of unsound mind. The patients should be fed at regular intervals, and surrounded by persons who have moral control over them, relations and friends being generally the worst attendants. Food should be administered at intervals varying inversely with the exhaustion and emaciation. The inclination of the patient must be in no way consulted. In the earlier and less severe stages it is not unusual for the medical attendant to say in reply to the anxious solicitude of the parents, 'Let her do as she likes. Don't force food.' Formerly I thought such advice admissible and proper, but longer experience has shown plainly the danger of allowing the starvation-process to go on."

It is of interest to see how fully Gull understood the recognition

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and proper management of the clinical entity to which he first gave the name anorexia nervosa.

There have been many observations concerning the physical and physiological aspects of anorexia nervosa. There is extreme emaciation. The skin is dry and scaly. The temperature and the blood pressure are low, and the pulse slow. X-rays of skulls and sella turcica show no evidence of expanding pituitary lesions. The extreme emaciation is always associated with amenorrhea. The vaginal smears show an atrophic type of smear. With a gain in weight and general improvement the smears approach that seen in normally menstruating women. Some report lowered metabolic rates, and others report flat curves with the glucose tolerance tests during periods of emaciation, and normal curves after improvement and an appreciable gain in weight. There is usually constipation.

Farquharson and Hyland[2] have given in great detail the differential diagnosis particularly as concerns Simmonds' disease which is due to extreme insufficiency of the anterior lobe of the pituitary. Simmonds' disease occurs most frequently in adult women who have had several children, beginning usually in the puerperium after a difficult labor associated with sepsis, postpartum hemorrhage or some other complication. It also occurs when the anterior lobe has been destroyed by tumor or trauma. The physical health and personality structure have been previously considered adequate and good. Anorexia nervosa occurs in adolescents and young adults and in older people with previous neurotic difficulties. In Simmonds' disease the loss of appetite is unassociated with emotional attitudes, while in anorexia nervosa the anorexia is associated with a morbid aversion to eating. The amenorrhea of Simmonds' disease is associated with loss of secondary sexual characteristics, falling out of axillary and pubic hair and atrophy of the sexual organs. The 17 ketosteroid level in Simmonds' disease is very low; in anorexia nervosa it is in the low normal range. The basal metabolic rate is much lower in Simmonds' disease, the blood sugar is lower, and there is almost always an anemia of moderate severity. The most striking differences are noted in the mental status. In Simmonds' disease the patient is dull and apathetic, whereas in anorexia nervosa the patient is generally alert, restless, wilful and impulsive.

Psychiatrists[3-5] have reported in the family background early dynamic factors and the personality problems encountered in patients

suffering from anorexia nervosa. All agree that the anorexia is not merely a passive loss of appetite but that there is an active morbid aversion to eating. Most all the patients show at some time compulsive and obsessive features with perfectionistic trends. The usual intensification of conflicts and disturbances of eating occur in relation to maturing sexually and to adolescence. The patients' mothers are tied into the psychological problems and there is usually great concern about food, diet, and proper eating on the part of the mother. This is naturally greatly exaggerated by the progress of the disorder in the patient. Some note that eating becomes equated with sexuality and growing up and oral impregnation fantasies. Rose,[6] in discussing eating inhibitions in children, shows that these individuals dread giving up old patterns and moving into new forms of psychological integration. There is apparently a resistance to and fear of change. Many patients voice a repudiation of sexuality and express a fear of the opposite sex. Many express a wish to die and indicate that the starvation holds in check what they consider the gross, physical or animal in their nature. Others have noted that the underlying dynamic structure of the personality resembles that found in patients with addiction problems.

Apparently there are varying degrees of seriousness in this reaction as seen in general practice, psychiatric practice, and in mental hospital experience. It is commonly noted by school physicians that young girls at boarding school are frequently disturbed by homesickness to the extent that there is loss of appetite, sleeplessness, loss of weight and amenorrhea of many months' duration. As a rule the loss of appetite is not associated with an aversion to food and the girls are able to see the entire emotional state as directly associated with homesickness. As the girl adjusts, the appetite, the weight, and the menses return. Certainly such reactions are not considered to be in any way a manifestation of anorexia nervosa. Among young girls and women who are refugees the upset state caused by leaving familiar surroundings and security is associated with varying degrees of loss of appetite, weight, and amenorrhea.

In our experience with patients suffering from anorexia nervosa we are certainly impressed with the fact that we are not dealing with a mild or partial reaction. Although all of our patients have been diagnosed as suffering from psychoneuroses of either hysterical or obsessive and compulsive types before coming to the hospital, and even

by some of the staff after admission, the clinical course of the patients who come to us strongly suggests that the reaction is profound, total, and sweeping in character.

The ten cases studied in this hospital represented the consecutive admission of such patients from 1938 to 1953, a period of fifteen years. These ten patients, girls and women, were between the ages of sixteen and thirty-eight at the time of admission; the average age was twenty-five. They came of unstable families. Seven had mentally sick parents and in one case both the father and the mother developed psychoses when the patient was maturing sexually. Two of the fathers were alcoholic. Another lost her father at the age of fourteen, and another's father deserted the family when the patient was four. It was difficult to evaluate the solicitous mother, since by the time the patient came for treatment the solicitude had usually been justified by the serious physical plight of the patient. In all patients the mother and the patient's psychic representation of the mother were definitely involved in the picture from early days. In all cases there was a peculiar dependence upon the mother, a wish to hold the mother responsible and at the same time a desire to be independent of the mother, resentment and even strong feelings of envy and jealousy toward the mother. The early trends and those studied after admission revealed a hostile and spiteful attitude toward the mother; indeed if one listened carefully some of their ideas about their mothers were delusional in nature.

One patient was attached to her mother who suffered from heart disease. The mother talked of dying, usually in the setting of great anxiety about the patient's physical state. The patient developed a fear of her mother's dying first but in fact the patient, who was admitted in extremis, died of exhaustion on the fourth day of her hospital residence.

The patients came from small families. In the ten families, including the preceding two generations, there was no preponderance of either sex. Three of the patients were only children, three had only one sibling, the other four came of families of two or more siblings.

They had been small babies and two of them were premature. All showed feeding difficulties, colic, and resisted changes to solids and a variety of foods. They apparently had serious times with childhood diseases. Three had complications of middle ear infections, one had a tracheotomy during an attack of diphtheria. One had a strabismus

which was corrected. All seemed to have more than usual trouble at the time of tonsillectomy.

A similar story of the infantile period was noted in a third of the cases in a study of 100 women patients with schizophrenia studied by Dr. Hamilton and the author in 1948. The experiences were traumatic and apparently weakened the ability to relate to others and interfered with achieving a feeling of belonging to the group.

As a group they moved from one level of adjustment to another with difficulty. This was manifested in early eating habits. They did not get along well with other siblings and found making friends outside the family group not easy. They were sensitive, shy, chubby little girls when they started to school. In their perfectionism they were rigid and did not accomplish too much. The obsessive and compulsive traits were not associated with too much anxiety.

The desire not to grow up and move on to succeeding levels of adjustments became particularly noticeable at the time of maturing and beginning adolescence. In a definitely recognizable fashion the theme of renunciation and denial came into their life symphonies as it were. Menstruation, growth and rounding out of the body and emotional stirrings of the time were rejected. To eat, to be fat, to grow up into life's responsibilities became disgusting, and with this there was a gradual withdrawal from life and relation to others. As a group they were shy with boys and they could not accept the sexual function of the mouth as in kissing which was disgusting to most and usually associated with some degree of nausea and vomiting. In none of the cases were there oral impregnation fantasies. In the majority of the cases at the very beginning of the difficulty there were varying periods of overeating, gorging and vomiting. Eating in some way became equated in a peculiar way with sex life. With the renunciation, denial, and withdrawal themes, aversion to food accomplished a destroying of life and sex, kept them from growing up and firmly opposed the thriving of what apparently was interpreted by them as coarse, animal-like and disgusting. One patient, twenty-one, after having had symptoms for several years, attempted marriage; immediately after the ceremony and the wedding kiss she took to her bed and expressed a longing for death.

Although all showed the early chubbiness and the disturbances of adolescence, only two were admitted under the age of twenty. Of the eight over twenty only three were married and of these only two

had children and for the latter two the great exacerbation of symptoms came during and after the first pregnancy. The other six were in their early twenties but had had symptoms of anorexia nervosa since adolescence. Most were under treatment for many years. All had been treated in general hospitals, and six had been treated in other psychiatric clinics. The average duration of illness for the group prior to admission was six years.

All were admitted because of the parents' or relatives' anxiety about the emaciation and withdrawal from life. Physically they were underweight, varying from 52 pounds to 94 pounds, the average weight being 80 pounds. Amenorrhea was present. In these patients the secondary anemia was serious. The basal metabolism rate was low, averaging -15. The skull x-rays showed normal pituitary fossae.

As a group they were restless, overactive and slept poorly. All expressed an extreme aversion to eating, something different from a mere loss of appetite or desire for food. Some seemed obsessed with the idea of food and eating but expressed an inner feeling of being opposed to taking nourishment. Some spoke of a wish for, and a fear of food and eating. All expressed a disgust for excess weight. Most expressed a desire not to take on the increasing responsibilities as well as the pleasures and privileges of adult life. All showed marked ambivalence about all the people in their lives. "Actually I do not know how I feel about any of these people (including relatives) that we talk about," said one. Others spoke of wishing to remain young and never grow up. Some spoke of a lack of direction and uncertainty in all spheres of their lives. More than one spoke of their "lights having gone out" and of having no feelings of depth. As one put it, "I never feel that my laugh comes from the heart."

All behaved in the same way about food. They would not eat without urging, would hide food in their clothing if possible, only to throw it away in the toilet later, and if at first they did swallow much food they would vomit soon after. They would cry as they sat and looked at their food, particularly when supervised. They played all kinds of tricks such as putting off bowel movements on the days before weighing, even though complaining of constipation and begging for enemata. Others hid weights in their slight clothing at weighing time.

Although the patients are alert, restless and overactive, feelings are not very warm or deep. There is a shallowness and apathy that goes

along with the patients' complaints of a lack of feeling and the uncertainty of their feeling except that associated with their aversion to food. In the withdrawn state the feelings strike one as being flat.

Dr. Mary Alice White, of the hospital's psychology department, has observed through the various tests that the common signs are those of withdrawal and flatness of affect. The patients react with shock and disgust to male and female sexual symbols on the Rorschach. The Rorschach responses are similar to those seen in alcoholics and addicts. There is much oral preoccupation, the responses are simple and there is much reference to sea life. According to the Rorschach interpreter there is a rather infantile personality structure with a lack of complex emotional responses.

The reaction, anorexia nervosa, is rarely seen in young males but young men suffering from serious alcoholism or addiction frequently exhibit a personality structure similar to that observed in girls suffering from anorexia nervosa. Many of these men give a history of early sensitiveness and withdrawal from reality. Excessive drinking of a solitary nature beginning in early adolescence is common. They wish oblivion and crave escape and even self-destruction. The drinking appears to help them temporize with many adjustments and life problems but eventually removes them from responsible living just as the refusal to eat brings about the withdrawal from life in the serious cases of anorexia nervosa.

As to the psychiatric diagnoses, these patients are called hysterias, obsessive compulsive states, depressions, and schizophrenias in various clinics. Certainly some of the patients who do not reach mental hospitals may be classified as neurotic or depressive reactions but those who reach mental hospitals after years of illness and treatment impress the workers in this clinic as suffering from a serious, profound, total and sweeping reaction. Patients can die of this condition and in many instances the emaciation has reached serious proportions when they come to a mental hospital. It has been said that these patients seem all right except for their attitude toward food. Indeed their attitude toward food is delusional in nature but there are many other signs of simple schizophrenia including their inability to relate to others, their lack of sustained drive even with the hectic restlessness and alertness plus the flatness of affect and withdrawal. One of the patients was thought by some to be suffering from paranoid schizophrenia and she

is one who has not done well. Another was thought to have a catatonic episode but the lack of drive and sustained effort were the outstanding clinical features in these two patients.

The following illustrative case history is presented:

A girl of 16 was admitted to the hospital on December 16, 1940 because she had refused to eat and adjust at boarding school. She came of English stock. The paternal grandfather was a quiet, "hen-pecked" man who for a period of eighteen years never spoke to his wife except in short quarrels. Their only son, the patient's father, was inhibited, dominated by the mother and divorced the patient's mother after six years. The mother was mildly depressed for many years and being employed spent little time with the patient. The mother had eclampsia during the seventh month and the patient, their only child, weighed only four pounds at birth. The patient developed normally but the father separated from the mother when the patient was four and divorced when she was only six. The maternal grandparents moved in and the mother went out to work. When the father left she spoke sadly of having no father and that he was not really her paternal parent. At seven she had temper tantrums and expressed the wish to be a boy. She enjoyed camping and won prizes for being a good camper. She cared little about her personal appearance and was never at ease with strangers. The temper tantrums followed her father's remarriage and after this for three or four years she overate. She hid food under her bed in order to eat at night. The abnormal eating continued to the onset of her present illness. Her grandfather died when the patient was eleven and when the patient was fourteen she lost her grandmother who had been the chief source of affection and care. She was plump but the next summer at camp she dieted and lost 12 pounds. She ate less and concealed food at table in her napkin. She became obstinate, refused to sit and could not study. She was hospitalized for one month in a sanitarium where she refused food and lost weight. She was in the Payne Whitney Clinic from February 12, 1940 to September 19, 1940. At that time she had amenorrhea. She was active and walked restlessly about, a pedometer showed eight miles of walking in one day. She ate under supervision and gradually gained a few pounds. She showed a paucity of trend. "I am all right. I am not sure about anything I say. I don't think. I don't know what you mean by thoughts." She took part in all the activities but continued vague,

restless, and when discharged she was sent to a boarding school in Maryland. At school she was restless, refused to eat, did poorly in her work. The principal wrote of her, "It seems to me there is a definite conflict between her desire to grow up and to stay a child. The other girls noticed how she did not want to have her hair fixed in a way that would make her look older, that she did not want to do the various little things that they like to do to show that they are approaching adulthood, that she preferred being with younger children and said she wanted to stay like them and did not want to change. On the other hand, she had the natural yearning of one of her age to attract boys and this seemed to be brought out by the school dance. It seemed that it was after this that the conflict became serious and interfered with her eating." She was brought from this school to the New York Hospital-Westchester Division on December 16, 1940, less than three months after leaving the Payne Whitney Clinic. On admission she was emaciated and pale. The laboratory studies were normal including x-ray of the pituitary fossa. Several B.M.R. determinations were above 20 per cent but at all times she was somewhat frightened, restless and uncooperative. There was amenorrhea. She was unkempt and extremely overactive, wishing to walk and keep moving. She was vague and shy and talked in a broken fashion. "I didn't know I was coming. I guess I lost a lot of weight. I didn't know I was going down and down and down in weight. I just love to—it makes me feel good." Her affect appeared blunted. She gave the appearance of eating well from a tray but lost about 6 pounds. It was discovered that she had been slipping food from the tray into her sweater and later tossing it into the toilet. Tube feeding was instituted and insulin treatment was administered. After six weeks in the hospital she had reached a weight of 101 pounds. She was on a full program. She talked of her parents' divorce and the loss of her grandparents. She had felt deserted. After six months in the hospital she prepared and passed her algebra Regents' examination and took up the study of English and the piano. She was able to spend some of the summer at the beach. She frequently had dreams and nightmares about death.

The psychological tests showed superior intelligence. The Rorschach responses were characteristic of simple schizophrenia, simple, unimaginative, with many references to sea life, sea horses, crabs and lobsters.

After a year in the hospital she became increasingly upset and

obstinate again. She attempted to run away but was apprehended. After about eighteen months in the hospital she was unimproved and was transferred to the Hudson River State Hospital on July 3, 1942. She continued under treatment with about the same type of behavior. She was restless and resistive. She talked little, "I guess I became run down and I wasn't eating." At times she appeared bewildered and showed blocking. The physicians of the Hudson River State Hospital thought her reaction to be catatonic schizophrenia. After one year in the State Hospital the matter of her leaving was discussed but she became upset, wept a great deal and she was kept under treatment with ground privileges for another year.

In the Fall of 1944 she went home to live with her mother. She has kept a large garden, raised chickens, shopped for neighbors, and has been partially self-supporting. She continues to be rather childish and her letters to Dr. Burdick show an interest in the people and the world around her to be that of a very little girl.

The treatment of these patients requires separation from their families and careful management in a mental hospital. They must grow up again, as it were, in an environment with people who afford a security which they apparently have not had. They appreciate a kind but firm attention. The average hospital residence was 11½ months. One was under treatment in this hospital for twenty-seven months. They must be tube-fed to combat the emaciation and ambulatory subshock insulin therapy up to 35 units is helpful. Electric shock therapy usually hastens the improvement. The varied hospital program activities of physiotherapy, occupational therapy, physical education, and social activities overcome the withdrawal and asocial tendencies. With the rise in self-esteem and self-confidence they become more responsive to psychotherapy. There is usually a paucity of material but a review of their personality development brings out the insecurity and fear of growing up and being a responsible adult. Reassurance and gentle but firm persuasion to keep up are the principles which appear to work. As a rule they make rather limited adjustments and many of those who come to us require further help in the way of supervision and careful allowance for their limited powers of adjustment and maturing.

Of the ten patients, seven have continued to do fairly well including the patient whose case history has been presented. Most of them live

rather limited and protected lives, oftentimes leaving their work for periods of rest. One patient died. The two others have continued to have difficulties and are under almost continuous medical care. One patient has so far made an excellent recovery and is fully employed. She is the last patient discharged, having been out of the hospital fourteen months.

All of them continue underweight and find it difficult to achieve a weight over 100 pounds.

The following letter is characteristic of the patients' adjustments.

"Although———— has not maintained the gain in weight which she acquired while at the hospital, she has for more than a year maintained the level to which she dropped during the first six months after her return home. Generally speaking her physical health is good and I am happy to report that she has retained a fuller appreciation of the factors which she must guard against to avoid the extreme underweight condition which prevailed prior to her stay at the hospital. I believe it reasonable to forecast that she has a sufficient realization of the fundamental requirements to maintain the status she now enjoys."

The patients with anorexia nervosa continue to be a challenge to all who work with them. The physiological and psychological manifestations are interesting but the restoration even to limited adjustments of individuals who have such a profound and sweeping disorder is most rewarding to all on the therapeutic team of the hospital.

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VASCULAR DISTURBANCES ASSOCIATED WITH FRACTURES*

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THE vascular disturbances associated with fractures constitute a fascinating group of problems. In some instances these disturbances are fraught with grave consequences, so that their early recognition and the institution of proper treatment are of paramount importance. In wounds of the extremities involving a major artery, DeBakey and Simeone[1] in World War II, found an incidence of amputation of 50 per cent. In the Korean conflict the application of newer blood vessel techniques to the problem of major arterial repairs resulted in a reduction in the amputation rate to 17 to 22 per cent.[2,3] While the problem of arterial damage is encountered less commonly in civilian practice, its consequences are such as to require us to be alert to any new techniques which may save limbs and yield better functional results. With this in mind let us consider first the immediate disturbances in arterial supply to the injured extremity and then follow with a short review of some of the remote changes.

The early troubles are of three types: 1) injury or division of the main artery of supply to the affected extremity; 2) compression of the main artery by hematoma or occlusion by angulation; and 3) severe vasospasm simulating occlusion. The signs and symptoms of impaired blood supply of the extremity are well known and consist of pain, coldness, numbness, pallor, empty veins, absent pulses, and with the passage of time, dependent lividity. Oscillometric readings are markedly diminished or absent distal to the occlusion. Naturally, the general condition of the patient affects these signs and symptoms. For example, a small degree of obliteration may be markedly accentuated by a shock-like state of the patient. Further, the pre-existence of any degree of obliterative disease may set the stage for obstruction

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and a check of the vessels in the other extremities may yield information regarding the initial state of the artery.

If it is apparent that the blood supply to the extremity is impaired, it is desirable to try to evaluate the role played by spasm. This is best done by some form of nerve block designed to interrupt the sympathetic fibers to the extremity. If the result is a very dramatic improvement in the appearance of the extremity following block, then obviously spasm is playing a dominant role and continued observation is justifiable with further efforts directed at the release of spasm. If, however, the result is slight, or if there is considerable hematoma or other reason to believe there is compression of or actual injury to the artery, exploration of the vessel should be considered. Before undertaking such a procedure, however, it is wise to have some idea of the consequences of sudden occlusion of major vessels untreated by surgery. According to four different authors, Wolff,[4] Makins,[5] Heidrich,[6] and Haimovici,[7] the incidence of gangrene ranges as follows: axillary artery 10-15 per cent, brachial artery 3-4 per cent, aorta 55-100 per cent, common iliac artery 40-100 per cent, external iliac artery 11-17 per cent; common femoral artery 22-26 per cent; superficial femoral artery 10-14 per cent, popliteal artery 15-37 per cent. With some understanding then, of the consequences of occlusion at different levels and bearing in mind that most explorations may be carried out under local anesthesia, where the patient's general condition is poor, and also bearing in mind that the extremity vessels are fairly readily accessible, the presence of perfectly obvious impairment of arterial flow requires exploration at the site of injury. Adequate blood for transfusion should be available, of course, for any blood vessel operation.

If the signs indicate that the vessel may be ruptured or if there is a large hematoma present, particularly if the latter pulsates, one should adhere to the fundamental vascular principle of obtaining careful control of the main artery above and below the area of hematoma before dissecting into it. Otherwise, with the first few cuts into the fascial compartments containing the hematoma, the release of tamponade pressure may be followed by a sudden gush of blood and considerable ensuing hemorrhage. The latter results in frantic and awkward attempts to control the bleeding and may be associated with undue blood loss. If, on exploration, the vessel is ruptured or badly trauma-

tized, the injured segment should be excised and either rejoined with end-to-end anastomosis or replaced with a prosthesis. The latter may be of three types, either 1) autogenous vein, 2) preserved homograft, or 3) a plastic cloth tube of suitable material such as Vinyon-N or Dacron, both of which are now under investigation as vessel replacements. If the injury is slight, lateral repair may be attempted provided it does not appreciably reduce the lumen of the vessel.

When neither a homograft nor plastic cloth prosthesis is available, then one will be forced to consider the use of an autogenous vein. Usually, a suitable vein can be found of proper length. It should be slightly smaller in diameter than the artery it is to replace since veins distend somewhat when filled with blood under arterial pressure. If the graft selected is already of the same diameter then it will be larger than the artery when carrying arterial blood, and form a fusiform dilatation which tends to propagate into an actual aneurysm. The vein segment should also be valve free, if possible, in order to prevent eddy currents which encourage the settling out of thrombi. The disadvantages of veins as grafts are aneurysm formation and thrombotic occlusion, particularly when long lengths are used.

If the blood vessel to be replaced crosses a joint or flexion crease, many have thought that the prosthesis of choice is a preserved homograft. Such arteries have already been shown to function nicely as replacements.[8-11] One barrier to the use of homografts lies in their scarcity, unless one has a large vessel-bank available with a wide variety of arteries. A second difficulty is that a few late blowouts have been reported in preserved homografts. A third objection is that sclerosis has appeared in the walls of such grafts two to four years after resection.[8]

Plastic cloth sewn into tubes of the proper diameter and length have been used by us to replace segments of the femoral and popliteal arteries. These cloths should probably not be used in vessels much below 4 mm. in diameter. We have had some experience with a cloth known as Vinyon-N[12] which has the property of retaining its tensile strength and which is markedly inert. It functions as a strut through the interstices of which fibroblasts grow to the inner lining surface where they assume a flat shape indistinguishable from endothelium. One objection to Vinyon-N is that the cloth now available has a high porosity through which a rather extensive blood loss occurs at the time of release

of the hemostatic clamps. Various other cloths have been employed in other parts of the country[13, 14] and efforts are now being made to study the different fabrics of Orlon, Dacron, Nylon, Vinyon-N and others in an orderly fashion, using comparable filament size, weave, twist, weight, and porosity. At the moment Dacron and Nylon cloths of low porosity appear to be suitable materials for blood vessel replacement.

If one should escape the immediate arterial difficulties, later complications are still a possibility. These consist in secondary hemorrhage, aneurysm formation, arteriovenous fistula, and so-called post-traumatic reflex sympathetic dystrophy. Any of us concerned with any volume of traumatic surgery has witnessed the frightful spectacle of massive secondary hemorrhage. This is commonly related to necrotizing infection and in this respect it is worth while calling attention to the gas forming organisms as possessing some potential for tissue destruction. Not infrequently life is saved in such cases by quick thinking ward attendants applying pressure at the proper point until the surgeon can be summoned. If infection is present, as it usually is, consideration of blood vessel replacement is out of the question and one is only concerned with controlling the hemorrhage by ligation of the vessel. This requires no special comment. Occasionally, however, the secondary hemorrhage may result from the rupture of an undetected or false aneurysm, secondary to the initial trauma. If this is the case, then replacement of the blood vessel by one of the techniques previously described is in order. Such an aneurysm might be suspected before rupture, if a pulsating mass is palpated in the region of injury. Should there be any question as to the diagnosis, this may be elucidated further by performing arteriography, providing the patient is not so immobilized in plaster as to make such an attempt out of the question.

An arteriovenous fistula may announce its presence by the appearance of dilated and tortuous veins with stasis pigmentation, dermatitis or ulceration distally, the presence of a thrill, palpable over the area of the fistula and the auscultation of a to-and-fro murmur, characteristic of such fistulae. Here again, if there is any question of the diagnosis, an arteriogram can be performed and may be of tremendous help. The treatment is surgical and depends upon the site of the fistula. Four point control must be obtained before any direct attack is attempted on the fistula itself. This means control of the artery and the vein

involved both proximal and distal to the fistula. Once this is done it may be possible to sacrifice the vein and to repair the defect in the artery with an over-and-over stitch. On the other hand, arterial repair may not be possible due to the size and shape of the lesion and it may be necessary to resect the fistula and replace the arterial defect with a prosthesis, as before mentioned.

Now, we come finally to a large group of disorders which may all be classified under the heading of post-traumatic reflex sympathetic dystrophy. When such autonomic disturbances are associated with severe pain, edema, skin changes, tenderness and hyperesthesia, they are called causalgias or the Weir-Mitchell syndrome. When they are associated with marked vasospasm, blanching and sweating of the extremity, they are called reflex, post-traumatic Raynaud's phenomena. And when they are associated with vasomotor disturbances and certain osteolytic changes in small bones they are called Sudeck's atrophy. In whatever form these disturbances present themselves, the underlying dysfunction is an autonomic nervous one. Here, it is worth while pointing out that the picture is not always a consistent one, but may be phasic. For example, a case of Sudeck's atrophy may, in the early period, present a picture of an erythromelalgia-like state with warm digits and a burning type of pain; later, this may be followed by a vasospastic picture with coldness, blanching and sweating. To me it seems less important to differentiate the different types of dystrophy than to recognize their existence early and to study their progression. Certainly, in those associated with causalgia type pain, it is well to interrupt the pattern early before the entire consciousness of the patient becomes fixed upon the pattern of pain. A regional sympathetic nerve block will quickly tell whether or not sympathectomy will bring relief, and if the causalgia is severe, a sympathectomy should be accomplished. Mayfield[15] has reported 105 patients with post-traumatic causalgia of the severe type, treated by sympathectomy, following World War II. In his series, all except nine were completely relieved of their pain. Other authors have reported smaller series with less benefit. In my own rather small experience I have observed a tendency for transferral of pain to other sections, even though relief of pain in the affected limb tends to be complete. This is particularly true in compensation cases.

In summary, some of the immediate and late vascular complications of fractures have been outlined. Some techniques of dealing with blood

vessels have been discussed. It is certain that the proper and timely application of such techniques to injured extremities will not only increase the number of limbs that may be saved after trauma, but will also improve the late functional results.

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THE EFFECTS OF TOBACCO SMOKING

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR G. JARVIS COFFIN: As you are aware, we are here this afternoon to discuss the physical effects of tobacco smoking. In a discussion of the strictly physical effects of tobacco smoking I suspect there will be so few proponents and supporters of the benefits of tobacco smoking that I, as an old hand at it, would like to say a few words in its behalf. First of all, it is pleasant, as many of us know who have enjoyed the pleasure of a cigar after dinner, on special festive occasions or at some family gathering. It is a sociable practice. It is relaxing to smoke in company with other people, and it gives comfort and solace, as we all know from the fact that in many of the war-torn areas the first request of a wounded soldier has been for a cigarette. But that does not alter the fact that we are interested this afternoon in the physical effects of tobacco on the human body.

The principal ingredient of tobacco is nicotine, so called from Jean Nicot, French Ambassador to Portugal in the sixteenth century, who received seeds from the West Indies and presented them to Catherine de Medici. The plant was attributed to have almost miraculous healing powers. At first it was called "Herba Panacea," "Herba Santa." Edmund Spencer called it "Divine Tobacco," and William Lilly, the astrologer, called it "Our Holy Herb Nicotina."

As you all know, tobacco is grown throughout the World,—as far north as the Province of Quebec, in Canada, and down through the Connecticut valley into the southern states and islands of the Carribbean. In South America it is grown as far south as Chile. It is also grown in southern Europe, in both North and South Africa and in many parts of Asia. The growing and processing of this plant have become a tremendous industry. Nevertheless the subject which we are going to discuss this afternoon is certainly a controversial one.

The opinions expressed this afternoon are the opinions of these gentlemen whom you see sitting up here before you. Our panel today is a group of distinguished gentlemen, each one a specialist in his own field of medicine, and it gives me great pleasure to introduce them: Directly on my left is Dr. Harold E. B. Pardee, Assistant Professor of Clinical Medicine, Cornell University Medical College, Attending Physician and Cardiologist, Polyclinic Hospital; next in order are Dr. A. Wilbur Duryee, Professor of Clinical Medicine, New York University College of Medicine, Attending Physician, Bellevue and University Hospitals; Dr. Herbert Maier, Assistant Clinical Professor of Surgery, College of

Physicians and Surgeons, Director of Surgery, Lenox Hill Hospital; and Dr. Ernest L. Wynder, Assistant Professor of Preventive Medicine, Sloan-Kettering Division, Cornell University Medical College, head of the Section of Epidemiology of the Sloan-Kettering Institute; and your moderator Dr. G. Jarvis Coffin, Assistant Professor of Medicine, Columbia University, College of Physicians and Surgeons, and Attending Physician and Director of Medicine at St. Luke's Hospital.

I would like to start with Dr. Pardee and ask him the first question. If I don't understand a word that any of you gentlemen use I am going to ask you to explain it. Some of you fellows have a jargon that even a medical man can't understand, and if you use an uncommon or obscure term, I shall interrupt and ask you to define that word or term.

Dr. Pardee, is smoking proven to aggravate angina pectoris—decrease coronary flow?

DR. HAROLD E. B. PARDEE: It certainly is. I do not know exactly in what percentage of people this occurs, but there are a great many people who have angina who are able to produce an attack of pain by smoking one or two cigarettes. The attack may be relieved in the usual way by nitroglycerine or it may pass off of itself if the smoking is stopped. It usually does not come on immediately but it comes on along toward the end of the time that the cigarette is being smoked. It does not, however, aggravate the fundamental condition in the coronary arteries which causes angina pectoris, although I think it does aggravate the diminution of coronary flow which results from the narrowed coronary arteries.

MODERATOR COFFIN: *Is that spasm, Dr. Pardee?*

DR. PARDEE: I believe that it is spasm. There are two theories as to how this pain is produced. One is that it is a result of raising the blood pressure and pulse rate; the other is that it is the result of a vasoconstriction of the coronary arteries. I believe the second is correct because of one interesting observation that was made by Wilson. He had a patient in whom the electrocardiogram, as a result of smoking one cigarette, assumed a form that we consider to be characteristic of a cardiac ischemia in the diaphragmatic portion of the heart. He put this electrocardiogram on a lag screen electrocardiographic setup so that it could be viewed continuously, and he found that during the smoking of a cigarette this peculiar feature of the electrocardiogram would appear for fifteen or twenty seconds, and then pass off, and then come back again.

That continued throughout the smoking of the cigarette and it stopped shortly after the smoking was finished. I cannot imagine that any increased cardiac work could have such a phasic incidence. It is much more likely that this was a vasospastic phenomenon which at one time caused less blood flow in this area of the myocardium, and at another time, with slight relaxation, allowed the blood flow to increase and allowed the electrocardiogram to assume a normal form.

MODERATOR COFFIN: *Dr. Duryee, in your opinion, what is the effect of smoking on thromboangiitis?*

DR. A. WILBUR DURYEE: I will tell you a story to illustrate the question put to me. As a house physician at the former New York Post-Graduate Hospital we had a senior attending who was much interested in the disease, thromboangiitis obliterans and, therefore, we were fortunate or unfortunate at that time in having a large group of these patients on the wards of the hospital. It was customary, as you made rounds, to note that the ash tray beside the patient was piled high with cigarette stubs. It has been recorded in the record room, that about 92 per cent of these individuals that came in with this diagnosis lost major parts of their extremities. In 1933, Maddock and Coller, working at Ann Arbor, were the first to observe that tobacco caused a high degree of vasospasm, and within a year a group at the Mayo Clinic emphasized the value of eliminating tobacco in the management of thromboangiitis obliterans. In 1934 at the University Hospital we started a vascular clinic, and from then on all patients who came in with this diagnosis not only at first were advised but later were forcefully requested to stop smoking. Between 1945 and 1950 a review of some 350 cases of thromboangiitis obliterans showed only an 8 per cent major amputation rate. The only significant difference in the management of these later patients was the elimination of tobacco. This story really gives you the answer. I could give many individual case histories which would indicate that tobacco is a major factor in the activation—I will use that word—of the disease. We do not believe that it is a causative factor; we believe it is an activating factor.

Just one final example: A patient with a diagnosis of Buerger's disease and with gangrene of one toe, stopped smoking in 1940. He did not smoke for ten years. He then resumed smoking and within three months had a massive gangrene in the other extremity. The disease was latent, but it was activated by the use of tobacco.

MODERATOR COFFIN: In connection with that, Dr. Duryee, may I ask you this question: *Is there anything that you can do for a patient with thromboangiitis in addition to his giving up tobacco?*

DR. DURYEE: Yes. Your question takes in the whole field of the prevention of thrombosis with our modern use of anticoagulants, it takes in the whole field of vasodilatation either on a drug approach or by reflex heat or by the interruption of sympathetic control. In addition to the elimination of tobacco one can use these modern tools of medicine and can accomplish a great deal more than we have done in the past. I made a statement a few minutes ago that these figures of amputation had been reversed, and that the only real change in treatment was the elimination of tobacco, and as far as Buerger's disease is concerned that has been the only real change in therapy. When you talk about arteriosclerosis and other thrombosing diseases then we have to utilize these other therapies. We rarely use anticoagulants in Buerger's disease. We rarely use vasodilators except perhaps for a few days or weeks when the acute episode occurs, so that the chief approach to therapy in Buerger's disease is the elimination of tobacco.

MODERATOR COFFIN: *Dr. Maier, here it comes. I am going to throw this one at you. As a surgeon who has seen a great deal of lung cancer, what is your opinion about cause and effect, that is between smoking and lung cancer?*

DR. HERBERT MAIER: It is my feeling that cigarette smoking is probably the main cause for the increase in lung cancer that has been noted in many parts of the world during the past two decades. You note that I speak only of cigarette smoking. I feel that my own observations would not justify me to make any statement in relation to other types of smoking. I think that one of the points that must be stressed is that much confusion has arisen because it has not been appreciated that there are various types of lung cancer. All patients with lung cancer should not be considered as having a single similar disease. The reason I bring this out at this point is because the smoking history of the patient with squamous or anaplastic carcinoma points strongly to the relationship with cigarette smoking, whereas the smoking history of patients with adenocarcinoma does not. Since adenocarcinoma is more common than squamous cancer in women, I would have no statement to make about the relationship of adenocarcinoma or carcinoma of the lung in general in women in relation to smoking. It is in the epidermoid or anaplastic

carcinoma, which is the one that has increased so tremendously in recent years, that we have the high correlation with this smoking history. Adenocarcinoma in men has become, percentagewise, less common because of the tremendous increase in the squamous or anaplastic carcinoma. Of course I do not infer by that that adenocarcinoma is less common in the lungs of men today than it was years ago, but because of the tremendous increase in the other forms it now assumes less prominence. Also, I would like to emphasize that I think that there are many factors that enter into the development of carcinoma, and when I say that I think that cigarette smoking has been the most important factor I want to emphasize firmly that I think there are many other factors, vulnerability factors concerning which we do not have information.

MODERATOR COFFIN: *Dr. Wynder, what is the incidence of lung cancer in smokers and non-smokers, and does the risk of lung cancer increase with the amount of tobacco consumed?*

DR. ERNEST L. WYNDER: The question as to the relative incidence in smokers and non-smokers could perhaps be answered by the statement that if it were not for smokers we would not be here today to discuss cancer of the lung because in population groups that do not practice smoking, lung cancer is a most uncommon disease. For example, in 1950, Dr. Dungal, of Iceland, who is a very good pathologist, recorded the incidence of various types of tumors in his pathological institute. Cancer of the lung ranked number nine in his autopsy series. Iceland did not take up the tobacco habit until 1945, and in 1945 the total tobacco consumption in Iceland was the same as it had been in England in 1920. To indicate to you how important a problem lung cancer has become today all I have to do is to tell you that lung cancer today constitutes the most common cause of cancer death among males in this country. In England it accounts for 25 per cent of all male cancer deaths, and within the age groups of 45 to 55 it accounts for 44 per cent of all male cancer deaths. In Vienna in 1951 it accounted for one-third of all cancer deaths in males. As I stated, lung cancer is a most uncommon disease among non-smokers. I have recently reviewed fourteen retrospective studies totalling more than 6,000 lung cancer cases. The per cent of non-smokers among these is 1.5 per cent. It is so unusual to see non-smokers with epidermoid cancer of the lung that we have recently written a paper about cancer of the lung in non-smokers. The relative risk of

developing lung cancer rises in proportion to the amount of tobacco consumed. The exact extent of the risk is difficult to determine but it rises somewhere between 15 and 50 fold over a non-smoker. Dr. Snagriff, of Harvard, believes it is in the neighborhood of 50 fold. In the recent study by the American Cancer Society Dr. Hammond and Dr. Horn believe it is somewhere between 10 and 20 fold. As more data are available on these prospective studies, we will have more data on exactly how much greater the relative risk is.

I agree with Dr. Maier that smoking, of course, is not the only factor causing lung cancer. Lung cancer, as I have stated, does occur in non-smokers, although it is rare. Obviously not every one who smokes does develop lung cancer; however, on the basis of the data that Dr. Graham and I have accumulated over the past four years we believe that 90 per cent of all lung cancers in men of the epidermoid type are associated with tobacco smoking, and that in the absence of tobacco smoking these 90 per cent would not occur. Translated in different terms, it means that if we had 20,000 deaths in males from epidermoid lung cancer last year 18,000 of these could be avoided should we be able to modify or reduce our smoking habits.

MODERATOR COFFIN: *Dr. Pardee, does nicotine cause electrocardiographic changes? Are they permanent or temporary?*

DR. PARDEE: Nicotine does cause electrocardiographic changes in a considerable number of people. In about one-third of normal people there will be changes in the T-wave amplitude, and in a few there will be changes in the direction of the T-wave so that it becomes inverted instead of upright. In a few also there will be changes in the AV conduction time, the time that the impulse takes to pass from the auricles to the ventricles. In people who have coronary disease the appearance of abnormalities of the electrocardiogram is of a different type and simulates more closely that which we are accustomed to find as a result of coronary sclerosis with myocardial ischemia in localized areas. It may, as in one case I mentioned before, simulate a small area of infarction. It may in other cases simply cause a depression of the ST segment such as we consider characteristic of coronary insufficiency. These changes are transient; that is, they last a short time after the smoking is finished, and as far as we know do not result in any permanent damage. I do not think it has ever been reported that they cause permanent changes. How long they last is not exactly known, but by analogy with what we know

about the duration of the tachycardia and the increase in blood pressure that result from nicotine it might be about 30 to 45 minutes. The electrocardiographic changes, as I say, have not been timed specifically.

MODERATOR COFFIN: *Dr. Duryee, what is the effect of smoking on the circulation of patients with peripheral arteriosclerosis? Does the amount of smoking make any difference?*

DR. DURYEE: The picture in arteriosclerosis is not as clearcut as it is in thromboangiitis obliterans. We know that certain cases of arteriosclerosis seem to progress and the blood supply becomes reduced at a more rapid rate in those individuals who continue to smoke, and in other cases smoking apparently has little effect on the progression of the disease. Dr. Aaron Kellner at the 1951 Graduate Fortnight of The New York Academy of Medicine made a statement in describing arteriosclerosis which may help us explain some of these variabilities. He called arteriosclerosis an episodic disease, and I think those of you who think back over the patients that you have followed with arteriosclerosis will readily recognize that in most instances we do not deal with a disease that is constantly progressing; in other words, there are episodes where occlusions take place. They may be cerebral, they may be in coronary vessels, mesenteric vessels or peripheral vessels. There may be long or short periods in between when there is no evidence that the disease is progressing. If the X factor which produces this progression is active, and if at that time the patient is smoking and adding, in addition to the progression of the disease from the natural cause of the disease, the vasospastic effect of tobacco,—then one may accelerate and complicate the disease of arteriosclerosis.

Dr. Kellner also described this disease as a segmental disease. If one pictures a segment of an artery involved with an occlusive process of atherosclerosis or arteriosclerosis and then a normal segment proximal to that diseased segment, and if the individual who smokes is particularly susceptible to tobacco and develops a degree of spasm in that normal segment, then one lays down the ground work for an occlusive process in the distal diseased segment. It is the custom of most of us who are working in this field to advise the individual who is suffering from arteriosclerosis to eliminate tobacco for the rest of his life because one never knows when this X factor, that causes a production or an exacerbation of the disease, is going to become active. Therefore, there is no way of saying,—you can smoke for the month of July but you must not

smoke in November.

One brings up the question as to the amount of smoking, and here we have almost a reversal of the problem as related to lung cancer. The maximum vasoconstriction effect of tobacco results from the first puff that the individual takes in the day. Most of you who have been smokers will have had the experience that on your first puff of a cigarette in the morning you may get a slight feeling of giddiness or dizziness which will not occur with smoking during the rest of the day. It has been shown by temperature changes and by plethysmographic studies of blood flow, that the first inhalation of tobacco smoke or introduction of nicotine into the body causes this very high degree of spasm. Then the pharmacologic effect of the nicotine gradually tapers off as the day goes along so that the actual amount of smoking is not a big factor. It is that first puff that you take in the day that does the damage and you can't take the second one until you have had the first.

MODERATOR COFFIN: *Dr. Maier, would you be good enough to discuss early diagnosis of cancer of the lung, with special emphasis on sputum examination and x-ray?*

DR. MAIER: I shall first discuss the x-ray examination because that is by far the most important step in the early detection of cancer of the lung. Since many a patient with cancer of the lung is entirely free of symptoms for months or sometimes even longer periods of time while the cancer is growing, it is obvious that if we wait for symptoms to develop most of the cases are too advanced for surgical removal. Thus at the present time the best recommendation we can give is that smokers have a chest x-ray twice a year. It must be realized, however, that the interpretation of small early abnormal shadows in the lungs is a difficult matter and too often small shadows that are seen which are actually early cancers of the lung are erroneously interpreted, even by the most experienced, as some minor lesion of no particular significance. So the problem is not just limited to taking the x-ray but includes the sometimes greater problem of interpreting what is seen on the film. It is true that in some patients the cancer of the lung may manifest itself reasonably early by some increased cough or slight blood spitting. The cough is usually not helpful because most of the patients with lung cancer have had a chronic cough from their cigarette smoking for years previously so that they tend to overlook a slight increase in cough. The most minute blood spitting would be an indication for an examination, and in

that group sputum examinations properly done could be helpful. I say "could be helpful" because at the present time they play a small role, first, because the specimen must be truly representative and come from a case that is sufficiently advanced to have an ulcerating lesion that will shed cells in the bronchial tree and, second, it must be collected in such a way that the cells have not deteriorated before the cytologic examination and, thirdly, and by no means least, is the still very limited availability of people trained to make these cytologic studies. At the present time, numerically speaking, we get more help from the secretions aspirated at bronchoscopy when these are subjected to cytologic study than from sputum examinations. Of course that entails the major procedure of bronchoscopy which cannot at present be applied to the population in general.

MODERATOR COFFIN: *Dr. Maier, did you mention the overall prognosis of operable cancer of the lung? Can you talk about that for a minute?*

DR. MAIER: That is a distressing subject and when I give you figures on that you will see why it is that a surgeon who sees many of these patients may feel that he can do more good by talking about ways in which the disease might be avoided rather than what he can accomplish by operating upon such patients. If we consider all patients with primary cancer of the lung who are admitted to a good general hospital, and who have the best modern medical and surgical care, the five-year survival rate is likely to be something as low as 6 per cent or sometimes even less, so that you can see that the overall imprint of surgical therapy on this disease is small, when we consider that the disease has become so common in recent years.

MODERATOR COFFIN: *Well, that would go along with the theory that early diagnosis is the most important and that routine x-rays are almost imperative in smokers. Is that correct?*

DR. MAIER: Yes, but one must add that even in those routine x-rays there will be a certain percentage of cases that will already be found inoperable, and we have yet to determine how much improvement in the overall salvage we can even obtain by such a procedure.

MODERATOR COFFIN: *Dr. Wynder, I think you have already answered the first part of this next question. However, I will ask you again. Is there an actual increase in lung cancer, and if so, could this be due to industrial air pollution? Is lung cancer more prevalent in cities than in farm areas?*

DR. WYNDER: There used to be, up to a year or two ago, a good deal of debate whether the increase in lung cancer was real or apparent. I think that today, among people in the field, there is no longer any doubt that the most significant part of this increase is indeed real. The thing that has always impressed me about this increase is the fact that it has been primarily in the male, though recently there has also been a slight increase in the female. It used to be argued that this increase was primarily due to improved diagnostic means. Obviously women are exposed to the same diagnostic means as men are and this, therefore, could not account for the predominant increase among males. In this picture about increase, perhaps the most disturbing outlook is the fact that the statisticians tell us that the increase will continue. Last week we had as a visitor Dr. Clemmesen, one of the experts in this field, who works in Denmark where they have much better data on incidence than we have. He predicts on the basis of cohort studies, that the mortality from lung cancer in Copenhagen will increase five fold in the next fifty years. By the end of that time the total death rate from lung cancer among males will equal the total cancer rate today. You can well see that if such a prediction should also be true for the United States that we would have indeed a tremendous number of lung cancer deaths a few years hence. Dr. Morton Levine, of Albany, also predicts that the lung cancer incidence will continue to increase markedly in this country. I do not believe that this increase is due to air pollution, at least not to any significant degree. The reason for this is twofold: First, if air pollution were a major factor then the women in cities who are certainly as much exposed to city dust as the men are should have had a considerable increase in lung cancer also. The second reason is one which did not originate with me but originated again with Dr. Clemmesen, and was later worked out by Dr. Levine of Albany. It is a little complicated. It involves cohort studies in lung cancer. Lung cancer incidence, and the rates in different age groups, are peculiar in that there is a marked peak in the early fifties in lung cancer unlike that of any other major cancer, and then it declines. Dr. Clemmesen was one of the first to point out that this peak in the early fifties is compatible with a carcinogen introduced into our society some 30 years ago, which did not exist 40 or 50 years ago. Air pollution, if this were a major factor, was introduced to all age groups at the same time and, therefore, if air pollution were a major factor we would not note this par-

ticular age peak that we find in lung cancer. Lung cancer does occur more commonly in urban than rural areas, and it has been claimed by some workers in the field, such as Dr. Hooper, that this obviously had to mean that some air polluting agents in the city were responsible for this greater lung cancer rate in cities. Before you can use the word "obviously" in any statistical clinical study you must investigate all of the other possible factors. For instance, there are more thoracic centers in our cities than in our farm areas, and it is quite possible that many lung cancer patients who originally may have lived on a farm, may have moved into the cities to die there; but particularly, other possible variants between people living on farms and in urban areas must be investigated. Drs. Doll and Hill were among the first to investigate differences in smoking habits between people living in London and rural areas. They found there were about twice as many non-smokers among the farmers than among people living in London, and furthermore there were twice as many pipe and cigar smokers among farmers, and we have already learned that the relative incidence is greater among cigarette smokers than among pipe and cigar smokers. A few months ago Dr. Day, Dr. Bruce and I did a study among farmers in upstate New York. We found 35 per cent of these farmers to be non-smokers. We found only half that number of non-smokers in people that we interviewed in the city, and again there were more cigar and pipe smokers among the farmers. In this respect I agree with Dr. Doll of London that if you standardize for smoking habits then it makes no difference whether you live in an urban area or a farm area as far as your risk in developing lung cancer is concerned.

MODERATOR COFFIN: *Dr. Pardee, does smoking predispose to extrasystoles and tachycardia in the normal heart?*

DR. PARDEE: Tachycardia is one of the most common phenomena seen as a result of cigarette smoking in those with a normal heart, but less than half of the people who smoke show this. It has been suggested that a rise of 25 beats per minute should be considered as an indication of an abnormal degree of susceptibility or sensitivity to nicotine. Premature beats are also produced but not with the same frequency as tachycardia. Less frequent also are occurrences of such arrhythmias as sino-auricular block and auricular fibrillation, but they have been reported and probably occur occasionally.

MODERATOR COFFIN: *Dr. Duryee, what does smoking do to the normal capillary circulation?*

DR. DURYEE: Some of the original investigative work in the observation of capillary blood flow in relation to smoking was conducted at the Mayo Clinic and also at the New York Post-Graduate Hospital (now the University Hospital). It had been common practice to observe the fingernail capillaries under a microscope. It was noted that when a large capillary was observed for a period of about 120 seconds, or two minutes, the blood would cease to flow for at least 20 seconds. This occurs in a normal individual under ideal conditions; that is, in a room with the temperature constant, and with the patient resting. If an individual smokes, usually within a second or two after the smoke enters the mouth—and it does not have to be inhaled—there is a complete, sudden stopping of blood flow through the observed capillary, and that stoppage may last anywhere from a few seconds to as long as five minutes, the average degree of stoppage being between 75 and 80 seconds. This stoppage of the capillary blood indicates that, as a patient smokes, there is some blockage in arterioles supplying the capillaries. I have not time to go into a full explanation but the indications are that this spasm takes place chiefly in the smaller arterioles which feed the capillaries. It has long been known that the capillary itself does not have much power to go into spasm, that the opening in the capillary remains fairly constant regardless of the pressure in the rest of the system, and the terminal arteriole acts more or less as a dam which lets blood spill into the capillary loop. It is by this slowing of blood through the capillary loop that we felt that we were demonstrating vasospasm.

MODERATOR COFFIN: *Did you mention the fact, Dr. Duryee, that you could measure that on a plethysmograph?*

DR. DURYEE: You cannot measure the actual capillary flow by plethysmographic study. Lampson of Yale has done a study as have many others, including Abramson of Cincinnati. They have measured the blood flow through a finger, total blood flow, following the smoking of a cigarette. If one assumes that normally the finger has about 8 cc. of blood per 100 cc. of finger volume flowing through that finger, immediately after the smoking of a cigarette the amount of blood flowing through that finger often will drop down to 1 or 2 cc. per 100 cc. of volume. We have, therefore, another method of measuring blood

flow, but it is not of the capillary flow alone.

MODERATOR COFFIN: *Dr. Maier, I asked you this question before, but I don't think you have answered it completely. Would you care to discuss any further the prognosis of cancer of the lung?*

DR. MAIER: The prognosis is affected by the type of the cancer in that particular patient. We have certain pathologic types in which the prognosis is considerably better than in other groups. One of our worst groups is the young patient, a male, who is under 40 years of age, who frequently gives a history of having smoked over two packs of cigarettes a day, who often has a very rapidly growing anaplastic growth in which surgical therapy rarely is effective. At the other extreme, however, we have some squamous carcinomas that grow more slowly, and they are more likely to occur in a somewhat older age group, and in those cases we can expect far more from surgical therapy, so that we do have to consider what type we are dealing with in estimating the prognosis with and without treatment.

MODERATOR COFFIN: *Dr. Wynder, does smoking seem to affect one particular type of lung cancer? Is it true that most lung cancer arises in the major bronchi?*

DR. WYNDER: In 1950, in our work with Dr. Evarts Graham, we called attention to the fact that we thought that the association of smoking to lung cancer was particularly applicable to the squamous cell type or the anaplastic type of cancer and to a lesser degree to adenocarcinoma of the lung. In some further studies we confirmed this. When we recently analyzed 20 cases of non-smokers with lung cancers we found that six of these 20 cases had adenocarcinoma. This is a higher percentage of adenocarcinoma than you would expect from the usual ratio. I was able to collect a total of 41 lung cancer cases in non-smokers from other investigators, and the per cent of adenocarcinoma among these 41 cases in non-smokers was 29 per cent. Again this seems a somewhat higher proportion of adenocarcinoma among non-smokers than you would expect otherwise. On the other hand we also note more excessive smoking among our male patients with adenocarcinomas than among our controls, so that we currently believe that smoking also may affect the development of adenocarcinoma but if it does so it does so to a much lesser extent than the squamous cell cancers. Most of the lung cancers arise in the major bronchi. Various studies cite figures anywhere from 75 to 90 per cent. In the more recent studies

it seems that the lung cancers arise more commonly in the major bronchi than they did some ten or twenty years ago. The studies furthermore agree that the upper lobes are more commonly affected than the lower lobes: about 75 per cent of the lesions arising in the upper lobes. Of the two upper lobes it is the right upper lobe which is more commonly affected. It has been suggested by some that this might be due to the fact that the right upper lobe comes off at a somewhat straighter angle, and the particles might have an easier chance to localize there. It is certainly true that today the problem of lung cancer is one involving the major bronchi, and it is perhaps because of the location of these lesions that surgeons have such a problem. Because of the location, not only do we fail to obtain early indications on x-ray, but also because of their nearness to the lymph nodes, by the time we do pick them up metastasis is frequently already present.

MODERATOR COFFIN: *Dr. Pardee, I have a question from the floor for you.* 1) *How do you personally advise your patients about smoking?* 2) *What is the medical profession doing about smoking; and* 3) *What are the Departments of Health (municipal and state) doing about smoking from the municipal and state standpoint?*

DR. PARDEE: I would like to answer the third one first. I don't know what they are doing. The question as to whether or not smoking should be forbidden is one which I think has two angles to it. One is the character of the disease that the patient has and the other is the patient's susceptibility to reactions from nicotine. There are certain serious diseases, such as cardiac infarction, the result of coronary thrombosis or otherwise, and conditions such as rheumatic carditis, in which there is a marked tendency to tachycardia. You would not want to increase the tachycardia in these patients so I do not think that they should smoke. They are usually too sick to desire to, so it is easy. Patients who have heart failure have difficulty in getting air in and out of their lungs, and smoking, as we know, causes a certain degree of bronchospasm that would interfere with the passage of air, therefore, would not be good for these patients who have a tendency to heart failure. If this heart failure is due to coronary arteriosclerosis causing degeneration of the heart muscle, then there is another factor to be considered, and that is the tendency of the coronary arteries to go into spasm as a result of nicotine. That is a thing that we cannot exactly determine by any method that is available at the present time. You can,

however, determine the patient's reaction to nicotine as to the increase in heart rate which has been mentioned and blood pressure also. Some patients who have coronary arteriosclerosis can be made to develop angina by smoking. I do not know in what percentage this occurs—perhaps 20 per cent, more or less. These patients, of course, should not smoke because they develop a degree of myocardial ischemia which causes pain. Whether the other patients who, perhaps, do not develop tachycardia as a result of smoking should be considered to be immune to the nicotine effects or not, is doubtful, so any patients who seem to be susceptible should be advised to give it up. I would advise a patient who does not seem to be susceptible, to give it up for a while and see what happens to the angina. If improvement did not seem to coincide with giving up the cigarettes, I would then feel that he might experiment by smoking a relatively small number a day, say five or six cigarettes, and watch for an increase of the tendency to angina.

MODERATOR COFFIN: *Dr. Pardee, do you want to pass that second question: What is the medical profession doing about smoking?*

DR. PARDEE: I am one member of the medical profession. The medical profession is full of individualists, and I do not know what the medical profession as a whole is doing about it. I would say that in the long run and on the average it is probably handling it much as I have suggested in this discussion.

DR. DURYEE: Dr. Coffin, I would like to elaborate on that because of the action taken by the American Heart Association in Chicago about two months ago.

MODERATOR COFFIN: Go ahead.

DR. DURYEE: The executive or the staff in the main office in New York was being besieged by questions as to whether a person with heart disease should smoke, and the staff members were at a loss to give any sort of a reply, so they put it up to the Executive Committee of the Scientific Section to render an opinion as to what information the American Heart Association should give out from this standpoint. Actually, a committee of the Association is studying this problem, and the opinion reached in December was that we had insufficient information from a scientific standpoint at this time to come out as an organization with clearcut statements as to whether a person with heart disease should or should not smoke.

MODERATOR COFFIN: *That is helpful Dr. Duryee. I will now give you your regular question, the answer to which may be given in a few words: Should smoking be forbidden in Raynaud's disease?*

DR. DURYEE: That is not as easy to answer as you might think. From a purely scientific approach you would say this is the ideal disease in which to eliminate tobacco because we are dealing with a 100 per cent vasospastic disease, especially in the early stages. There are some other angles to this that are not as easy to get at as would appear from the surface. In the first place, Raynaud's disease, better known as Raynaud's syndrome, is often an early manifestation of an organic disease. In many cases a Buerger's disease will have this syndrome for a period of six months, or a year, or two years, before one actually can prove that organic disease is present. Therefore, in every case of Raynaud's disease there is always the possibility that this syndrome may be a manifestation of other vascular disease and therefore, smoking should be prohibited. Individuals who suffer from a so-called idiopathic or essential Raynaud's disease, where no primary cause for the disease is found, apparently get little relief from stopping smoking. In other words, the vasospastic effect of emotion, or especially cold, is so much greater than any other vasospastic effect that even eliminating smoking, which is a big one, does not alter the disease. I believe a simple uncomplicated case of a Raynaud's syndrome is probably not benefited or made worse by the use of tobacco.

MODERATOR COFFIN: *Dr. Maier, aside from carcinoma is there any respiratory hazard to smoking? In other words, do you believe heavy smoking contributes to chronic respiratory disability in asthma, bronchiectasis or chronic bronchitis? Are these respiratory cripples chiefly relieved by abstinence from tobacco?*

DR. MAIER: First, I think, it should be said that we have no evidence that bronchiectasis or most forms of asthma or many cases that are classified as chronic bronchitis have any relationship with smoking from an etiologic standpoint. I think the chief factor that determines whether a person who already has one of these conditions is worse off because he smokes is related to whether the smoking produces additional irritation and bronchospasm. Some patients who have these chronic pulmonary disabilities seem to be about the same whether they smoke or not, whereas in many others there is a definite improvement following abstinence from smoking. So that in cases that have such

chronic pulmonary diseases, and where the patient is a smoker, we may recommend a trial period and see whether temporary abstinence from smoking improves the patient. However, there is another group which has a chronic cough, perhaps with varying degrees of shortness of breath, which may be classified as having chronic bronchitis or may have varying degrees of emphysema also, and in many of these patients the symptomatology is largely related to whether or not they smoke. Recently several articles have appeared using the term of "smoker's lung" in referring to some chronic cough related largely to smoking, but I think it should be stated that, in general, it would seem that the presence or absence of symptoms is mostly related to whether cigarette or other types of smoking in that individual leads to bronchospasm or bronchial irritation.

MODERATOR COFFIN: *Dr. Wynder, does the use of tobacco have an effect on any other organs or human disease, and specifically may I ask you what is your opinion about the use of tobacco in a patient with peptic ulcer?*

DR. WYNDER: Most of the diseases about which we know a great deal, that is, about the possible relationship of smoking to their management or origin, have already been mentioned here. My own personal experience only extends to other types of cancers, and I think that in studies now being conducted at various institutes, we see that cancer of the larynx, and cancer of the oral cavity, and probably cancer of the esophagus are also closely associated with tobacco consumption. The allergists cannot agree as to what extent tobacco may play a part in certain allergic disorders. They are mostly isolated cases on record where a certain relationship has been found. Among gastrointestinal men there is fair agreement that smoking will not cause peptic ulcer, but I think they would all agree that in the management of the patient with peptic ulcer, the patient should stop smoking. There are, of course, always a few physicians and laymen who think that every human disorder is caused by tobacco, and virtually everything has been mentioned including mental illness. Of course, we have no data about any of these suspicions. At the present time, we must only regard those things as significant for which we have presented data this afternoon. Tobacco, however, has a very important effect on mice. This is actually not a part of this question but I thought I would mention it anyway. Now mice obviously are not humans, and mice, as you know, also

usually do not smoke. However, in an experiment which Dr. Graham, Miss Croninger and I conducted in 1950, 44 per cent of the mice painted with condensed cigarette tar developed cancer of the skin. You may well ask what is the significance of this. Surprisingly enough this experimental data seemed to make a greater impression on many of my medical colleagues than any of the clinical statistical data and many who had not previously done so, have now given up smoking. Others, of course, perhaps agreed with The New Yorker Magazine which joked that perhaps all of this proved that mice should not smoke. I should like to make a brief statement about what significance we think these animal experimentations hold. Animal experimentations in the field of tobacco and cancer are being done because they give us a tool, and probably the only available tool to identify specific cancer-inducing substances in cigarette, cigar, or pipe tar. We are currently engaged in fractionating cigar tar into many fractions. We hope that eventually we will be able to come up with a fraction or two fractions which, if removed from the tar, will make the tar less or non-carcinogenic. Although we do not know whether this will have any significance on the human cancer problem I am sure that our public health services as well as the tobacco industry would agree that we should try to have these materials removed from tobacco. It is along these lines that the mouse or the rabbit gives us a useful tool, and perhaps may be helpful in discovering a preventive measure in the lung cancer-tobacco problem.

MODERATOR COFFIN: *I want to hurry along because we have some questions from the floor that I think we should attempt to answer. Dr. Pardee, can you give us an opinion about filtered cigarettes?*

DR. PARDEE: The cigarette filters are of various kinds, as you know, and they seem to have different sorts of ability to filter out things. For instance, some filter out nicotine better and some the tars better, but it has been shown that if a cigarette is puffed by a machine in more or less the way it is smoked by an individual that about 20 per cent of the nicotine appears in the smoke, if you use an ordinary cigarette. Three different types of filters were tested in the chemical laboratory of the American Medical Association, and with all three types of these filters just about the same percentage of nicotine appeared in the puffed smoke as with the ordinary cigarette without filters. That may seem foolish, but it is not, because the tobacco in the cigarette itself affords a filter which is apparently just as good as the other things that were

put into the stubs of the filter cigarettes. There was, however, a fourth filter which contained a mixture of asbestos fiber and paper, and this reduced the percentage of nicotine in the puffed smoke to 8 per cent in the original form, but that form was rolled so tightly that the drawing of the cigarette, puffing, was difficult. The company then loosened it up a little to make it more easy to smoke, and with that degree of filtering it produced only 13 per cent of the nicotine for the smoker—13 per cent of the nicotine as against 20 per cent in the normal cigarette. That is some reduction, but that is not enough reduction to make much of any difference to the human mechanism because the tendency to tachycardia is just as easily demonstrated with these filtered cigarettes as it is with the unfiltered ones. Even a cigarette which has been especially bred to produce only one-tenth of the amount of nicotine that the ordinary cigarette contains, I mean to say a tobacco which has been especially bred by the Government experimental stations, this cigarette made of this tobacco will also produce the tachycardia with almost the same degree of intensity as the ordinary tobacco, so it appears that the filters or even the specially bred tobaccos are really not much better than the ordinary cigarette.

MODERATOR COFFIN: *Dr. Duryee, this is the last set question we are going to ask. The remainder are going to come from the questions asked by the audience. Once having developed peripheral vascular disease, can a patient hope ever to smoke again? Can you relieve the symptoms of the majority of your patients by removing tobacco from their lives?*

DR. DURYEE: The first part of the question can be readily answered by saying "no" because once the vascular diseases we talk about have been established they are never cured. The tendency toward exacerbation in Buerger's is ever present and the same holds true for arteriosclerosis. Many of these people do have relief of their symptoms by discontinuing the smoking of tobacco. In the advanced arteriosclerotic with rest pain who wakes at 3 A.M. in the morning and has to hang his leg out over the edge of the bed with his feet on the floor to get rid of the pain in the foot, very frequently just the elimination of tobacco will eliminate that pain. If the disease has progressed to a severe degree, then tobacco elimination may not do it, but in the early stages it will, so that many of the symptoms can be relieved, but that is too large a question to go into now in detail.

MODERATOR COFFIN: *Dr. Maier, I will ask you this one: Endarteritis*

obliterans and primary lung carcinoma are more frequent in men, but at present women smoke cigarettes as much as men or more, and yet these conditions in the female sex are rare. Do you agree with that, sir?

DR. MAIER: I believe that it should be emphasized that there are many conditions in which sex hormones may affect the probability of added carcinogens producing cancers. It is fallacious to assume that if women who have smoked for many years do not develop cancer of the lung in the same percentage as men, the connection between smoking and lung carcinoma is disproved. Many cancers of the body, such as the esophagus, stomach, and so forth, have different incidences in the two sexes and, therefore, I think that we have to be far more broad-minded and realize that the whole biologic setup of the individual may play a role in what effect some exogenous factor will produce. That is what I referred to when I spoke of and used the term "vulnerability". By that I mean a vast number of chemical factors of which we are relatively ignorant.

MODERATOR COFFIN: *Here is another one, Dr. Maier. Is there such a thing as the early diagnosis of lung cancer? In other words, when symptoms appear, isn't it too late for surgery?*

DR. MAIER: There is great variation. You may have a patient who has had symptoms for a number of months who has still a lesion that can be cured by surgical excision. At the other extreme you may have a patient who has no symptoms at all in whom there are already extensive metastases. We do have a possibility of eradicating the disease in certain patients who have symptoms, and we have to allow for the variation in the course of the disease. As a matter of fact, occasionally the ones in whom we know the disease has been present for a considerable period of time (as a result of previous x-rays) may turn out to be cases in which we will get a good five-year result because we were dealing with a slower growing cancer in that particular individual.

MODERATOR COFFIN: *Dr. Wynder, is smoking without inhaling as harmful as with inhalation of smoke itself?*

DR. WYNDER: We believe that smoking with inhaling is more harmful as far as the possibility of lung cancer is concerned, but this is difficult to establish statistically. We found that among the average male population in this city some 90 per cent of these who smoke cigarettes do inhale. It is therefore very difficult to establish statistically significant differences. Among pipe and cigar smokers with lung cancer we have

found inhalers more frequently than in the average population of cigar and pipe smokers.

I would like to add a comment on the question that was asked concerning lung cancer in women.

MODERATOR COFFIN: Go ahead.

DR. WYNDER: The people who ask this question are not familiar with the long latent period of lung cancer, and with the fact that there are few women in this country who have smoked for thirty years, which is the average number of years which our lung cancer patients have smoked. From the data already available in our studies we have no doubt that, as the young females grow and arrive at the cancer age and have smoked for thirty years, their rates of lung cancer will rise significantly.

A final comment about filters. I think that the filter people have a somewhat easier problem in the cancer field than in the cardiovascular field. As was pointed out by Dr. Duryee, with nicotine, the individual, if he is sensitive, will be sensitive, let us say, to 50 per cent as well as to 100 per cent of a given dose. In the cancer field we are, in view of the long latent period observed in the human as well as in the experimental animal, already working with a rather low potent carcinogen in the hope that if we can still further reduce its potency by another 30 or 40 per cent we may possibly bring it below the threshold level of being a carcinogen.

MODERATOR COFFIN: *Dr. Wynder, there is another question right along that line: Should the tobacco companies change the type of paper used in cigarettes?*

DR. WYNDER: A great deal has been written in the recent past about cigarette paper. I must say that I feel a little bit unhappy about this because I thought that the way it was presented to the American public was not quite "cricket". It was stated that cigarette paper contains benzopyrene, which, as we all know, is a significant carcinogen. First of all, this cigarette paper was burned at unnatural temperatures. Furthermore, the amount of benzopyrene that finally was identified in cigarette smoke, if indeed it is present, is only present in very small amounts. Such amounts, in our laboratory, do not induce cancer of the skin in mice, and I think a mouse is a good deal more susceptible to this material than is man. There is no evidence, therefore, that the amount of benzopyrene that may be present in either cigarette paper or in cigarette

smoke is sufficient to be of any significance as far as carcinogenesis is concerned. I do think the way a paper may play a role is not so much in the type of paper as in the burning properties that it gives to the cigarette. For instance, if you burn a cigarette wrapped in cigar leaves rather than in cigarette paper, you get quite a different tar. This is in part due to the fact that this material burns at different temperatures. I do believe that the major carcinogenic portions that we find in tobacco smoke come from the tobacco leaf itself.

DR. PARDEE: May I say a word about the tar?

MODERATOR COFFIN: Yes.

DR. PARDEE: This same series of experiments in the American Medical Association laboratory produced some interesting facts about the tar also. The ordinary cigarette delivers about 18 per cent of the tar in the tobacco in the puffed smoke; the ordinary filter delivers about 15 per cent; and the asbestos and paper filter which I mentioned delivers about 8 per cent, so there is a 50 per cent reduction, which may be of some value.

MODERATOR COFFIN: I recall when those cigarettes, that I think you refer to, Dr. Pardee, first came out—it was a good day's work to get any smoke out of one of them.

Dr. Pardee, it has recently been stated that the ballistocardiogram shows changes from the normal graph in cases of tobacco-angina with normal ECG's. Any comment?

DR. PARDEE: Except that I know little about it. I know that this has been reported, and it is possible. It is known that any patient who develops angina is likely to show ballistocardiographic changes. What effect the nicotine has, I don't know—except that it might cause angina.

MODERATOR COFFIN: *Dr. Duryee, is smoking contraindicated in recent thrombophlebitis of the leg?*

DR. DURYEE: There are some types of thrombophlebitis that have the same general pattern as the disease process in thromboangiitis obliterans or Buerger's disease. In that type of thrombophlebitis which has a great tendency to recur, I would say it is definitely contraindicated. In the thrombosis of superficial varicose veins, the problem is quite different, and whether tobacco is discontinued or not, I do not believe is important. In the thromboses of the deep veins, the major veins, I believe it should be discontinued because of the possibility of slowing blood flow in the arterial system to the extremity and, there-

fore, in the end result slowing blood flow through the major veins, which is one of the things we wish to avoid. Except for the superficial thrombophlebitis in varicose veins I believe it should be eliminated.

MODERATOR COFFIN: *Dr. Wynder, there is a sort of political tinge to this question, at least I recall something about "smoke filled rooms". Can a non-smoker be influenced by inhalation of tobacco smoked in a smoke filled closed room?*

DR. WYNDER: I recently received a letter from one of the anti-cigarette leagues asking me precisely the same question. The answer to this question is that we do not know whether it has any effect on the formation of cancer, but in view of what I have already stated about tobacco being a relatively weak carcinogen I would very much doubt whether the smoke that we inhale from what smokers may blow into our eyes and nose is of any significance.

MODERATOR COFFIN: That concludes this afternoon's questions and answers both from the members of the panel and from the floor. Personally, and on behalf of the Academy, I want to thank each one of you, Dr. Pardee, Dr. Duryee, Dr. Maier and Dr. Wynder, for your interesting and informative presentations.

ROBERT ABBE: FOUNDER OF RADIUM THERAPY IN AMERICA*

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At the end of the last century, two independent but closely related discoveries pierced the mystery of impenetrable matter and opened the door to vast new fields of knowledge. In 1895, Wilhelm Conrad Roentgen announced his discovery that invisible rays, produced in a vacuum by high tension currents, penetrated opaque matter and lighted up a fluorescent screen. In the following year, Henri Becquerel discovered that invisible rays, which could penetrate solid opaque matter and blacken a photographic plate, were emitted spontaneously from uranium compounds. Thus the Science of Radiology was born. Shortly thereafter, in 1898, Marie and Pierre Curie discovered and isolated a new element with this most extraordinary property of emitting penetrating radiations. To this new element they gave the name, "Radium."

At the time of these epoch making discoveries, Robert Abbe was a well known surgeon in New York City on the staff of the St. Luke's Hospital. Not quite fifty years old, he was engaged in an active surgical practice and had already made many contributions to surgical technique. He was a man of great sensitivity and was alert to all new developments. He was quick to recognize the vast possibilities of these new penetrating radiations. In 1903, less than five years after the Curies discovered and isolated radium, Abbe brought back a supply of this new element from the Curie laboratory in Paris to use in his surgical practice in New York. Thus, Abbe was the first to introduce radium into this country. With undiminished enthusiasm and by tireless efforts tempered by a keen sense of observation and a facility for interpreting observations scientifically, Abbe founded a new specialty of *radium therapy*, a specialty destined to play a major role in the treatment of cancer.

At the time he acquired the radium, Abbe had had no experience with this new modality, nor had anyone else in this country for that

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matter. At the St. Louis Hospital in Paris, Danlos had used radium initially for the treatment of lupus and other dermatological conditions. He was satisfied that radium had a restricted value. The only other medical information available at that time was the burn that Becquerel accidentally acquired on his skin in 1901 and the similar burn that Pierre Curie intentionally produced on his arm. Better progress had been made in physics. It was already discovered that three types of rays were emitted, designated alpha, beta, and gamma, and most of the properties of these rays were observed. There wasn't much more knowledge for Abbe to work with.

Today, in 1955, we take much for granted. Our knowledge of radium, its decay products, its radiations, its useful biological effects, its adverse effects, its dosimetry, and the problem of protection are all easily available to any medical student and are part of fundamental training. None of this information was available and very few facts were known in 1903 when Abbe first acquired his radium. Learning depended upon trial and observation. Even after 25 years of experience, at the time Abbe died in 1928, a universal dosage system of radium had not been established. Abbe had to begin at the very bottom, without experience, without precedent, and without knowledge.

From Abbe's early writings and lectures, it is clear that he made a special effort to learn about the physical properties of radium and the relation of these properties to biological effect. He knew that there were three types of radiations: the alpha particles, which carried a positive electrical charge, had a small radius of action; the beta particles, which were fast, light, negatively charged electrons, were the most important biologically; and the gamma rays, which he thought were neutral electrons, travelled with nearly the speed of light. From the very beginning of his studies, Abbe was convinced that the beta rays, the negative electrons, were the major force that accounted for all the biological effects of radium therapy. He knew that the impact of neutral gamma radiation on animal tissue generated secondary beta electrons and thus provided a therapeutic agent within the cell. In this analysis he was basically correct.

Abbe was aware of differences in strength of various samples of radium. Evidently, weight in milligrams was not strictly an accurate method of measurement. One of the earliest methods was based on the rate of time it takes to discharge the electroscope. One of Abbe's speci-

mens which he acquired from the Curies had a strength designated "300,000" but according to him this specimen was much more powerful than another denominated "1,000,000" which he acquired from the Germans. Abbe also suggested that comparable information about the strength of various radium specimens could be obtained from the degree of blackening of a photographic plate. The importance of the radium carrier was also recognized, a property that we would today call filtration. Abbe knew that glass, rubber, aluminum, and lead, all behaved differently in regard to the energy that the same amount of radium would emit through these substances. The confused state of the physical data must have been a serious handicap to Abbe in the clinical application of radium.

Because of the lack of adequate physical methods of measuring radiation, Abbe expressed his opinion that "No one who ventures to use it (radium) in practice should do so without first testing his particular specimen or specimens on his own skin. . . . He may best choose perhaps the inner side of the calf of his leg for this test. Let the application be placed on the skin, at three nearby spots, for different periods say, five, ten, and fifteen minutes for very strong specimens, or twice that time for weaker ones. The effect should begin to show in ten days as a dermatitis; itching, burning and perhaps blistering in the following ten days; subsiding and forming a dry crust during the third ten days. On the thirtieth day the crust falls from a smooth skin. This is about the usual effect desired to restore a simple keratosis, mild epithelioma or a wart. Having once experienced the very definite results of using his specimens he never loses the mental picture of its action, or rarely misjudges the requisite time of application to each patient." These instructions were published by Abbe in 1920. While this method would not be followed by any radiologist today, yet it is similar in principle to the concept of the erythema dose which for many years was the standard method of measurement of the biological action of radium.

Abbe was evidently not too well acquainted with the adverse effects of radium or with its hidden dangers. In an article published in 1907 entitled, "Illustrating the penetrating power of radium," there is a photograph showing a glass tube with 60 milligrams of radium bromide held by his fingers over a granite rock. While he demonstrated the penetrating power of radium through granite rock, it seems he overlooked entirely the biological effect of the same rays on his hands and

body. Again, in a paper read before the International Surgical Society in Paris, in 1920, Abbe states that, "One thing is certain, that the Beta ray, isolated, may be showered for almost indefinite periods upon the skin, with no deleterious effect. Not even erythema ensues after hours of pure Beta therapy, but a sense of comfort follows." Abbe did not know that he was doing himself great harm by exposure to radium in this manner. In later years he developed aplastic anemia, presumably from his long exposure to radiation.

Abbe was keenly interested in the biological effects of radium and performed many illuminating experiments on seeds, insects, and mice. Oat seeds exposed to radium for varying times and then planted simultaneously showed the effect of time of exposure. The longest exposed were killed, the shorter exposed germinated and died, still shorter exposed grew stunted, still less exposed grew less than normal, while some with a very small "radiumizing" were stimulated and grew above the normal. Caged ants with their larvae were exposed to radium and appeared unaffected except that after a month they were unable to rear their embryos while control series matured naturally. Young mice put in a glass jar in which strong radium was suspended grew weak after a few days, "got dopey", became paralyzed in their hind legs, and died in convulsions. The effect of radium on the human skin and on cancer of the breast was observed in a woman with advanced cancer of the breast in whom a radium tube was placed on the skin for several hours, then on a tumor nodule in the skin, and then buried in the cancer mass itself. The pathology was studied by the late Francis Carter Wood. It was found that, on the skin, radium caused a superficial necrosis of the cuticle with deeper devitalization of cells for longer applications. Where there was cancer underlying the skin, softening and devitalization of the cell nests nearest the radium took place. When the radium tube was thrust into the cancer mass, an area of destruction of not more than a quarter of an inch was found. Abbe believed that the energy of radium was dependent on the activity of electrically charged particles which had the power of penetrating animal tissues to various depths. He also remarked that the action of radium was similar to that of roentgen rays, ultra-violet light, and Finsen light but with a different rating as to energy, the radium being as many times weaker than the roentgen rays as it is stronger than the Finsen light in lupus and allied troubles.

The early part of this century was a time of many and great dis-

coveries and developments in electricity so that it was not surprising for Abbe to state that, "It is fair to say that science is about ready to admit that electricity is the basic force actuating animal life, energizing nerves and muscles, tactile sense and cerebration. The recent study of cardiography by electrical conduction, whereby disorders of rhythm and function of the heart can be studied a half mile from the bedside, stand sponsor . . . for placing the responsibility on correct electrical charges for normal action of our bodies and on disordered electric action for their variations." It seemed a simple matter to relate all biological phenomena to variations in the balance of electrical charges.

Abbe regarded the orderly growth and life of a cell as due to a balance of its positive and negative electric charges. A tumor composed of cells abnormal to the part was the result of a loss of some force; the balance had been disturbed. At this stage of growth, if electrons are supplied, a return to normal occurs. Thus, according to Abbe, "Growth composed of overgrown masses of cells returns to orderly growth permanently when given the exact dosage of negative electrons. . . . Growths to which too much is supplied undergo atrophy and, if excessively oversupplied, undergo death. We may assume therefore that the dosage must correspond with the loss." Abbe believed that the origin of life was due to vitalization of corporate material, that is, nitrogen, carbon, and oxygen, by electric stimulation, the electrons coming from friction of elements, or from atmospheric discharges, or from radium latent in the earth, or just electrons shot through space. Abbe went further in his philosophical speculation and considered the force in radium as "incorporated life" with the electrons being "imprisoned life released." Protoplasmic matter, according to Abbe, was endowed with one vitalizing actuating force, electricity.

In considering the essential characteristics of malignant disease, Abbe believed that it was the lack of harmonious action that showed in the development of any and every curious growth to which we gave the name of tumor. They were one and all altered cell growths exaggerating their normal activity and representing a disorderly unbalanced action out of harmony with the rest of the system. In an interesting development of this theory, Abbe remarked that it was a literary error to speak of diseased tissue when we spoke of tumor structures, that while this word, disease, may be rightly applied to tissues attacked by parasitic agents, calling the structures diseased as we would a tree attacked by

"blight", it was quite an error to apply the word to tumors, even though they may in the end be destructive. More properly, Abbe continued, we should look upon the mass of overgrown cells, which from habit we call tumors, as aggregations of cells which are enjoying the excessive freedom of growth, "an ecstasy of joy and growth such as comes to an imprisoned city scholar set free in vacation spirit." The riotous overgrowth of cells normal to the site of their growth constitutes a tumor or colony of healthy cells which have lost their balance or equilibrium in their relations to their neighbors. Abbe believed that malignant cells had no characteristics to distinguish them from non-malignant cells microscopically, physically, chemically, or in their response to radiant energy, but only in their groupings did they differ, with more active mitoses indicating more rapid growth.

As a basis for understanding the action of electrons on all cell tumors, Abbe chose the wart which he described as a massive overgrowth of cells, regardless of whether these cells came from the papillary layer of the skin or from the delicate layer of mucous membrane of the vocal cords. In both instances he believed the tumor was the same. If, in either case, the tumor is exposed to the action of radium for a few minutes, it slowly disappears, leaving no trace of its existence. The same electrons have played on the healthy cells about the tumor but only the weak overgrown structure has changed. Abbe believed that the action of radium was specific for these growths and that exact dosage corrected erroneous growth without damage to normal cells. As a dramatic illustration of this specific action of radium, Abbe cited the case of a young girl with extensive papillomatous growths of the vocal cords which caused the huskiness of the voice, then loss of voice, and finally obstruction to breathing. Radium was applied for thirty minutes. In three months, the warty growth was entirely gone and the voice was completely restored. There was no recurrence on observation five years later.

Another case which illustrated the specific action of radium and which also profoundly influenced Abbe's thinking about tumor growth was that of a myeloid tumor of the lower jaw which was not only cured by radium but was also restored to normal appearance. The tumor involved the left mandible in a 17 year old boy. The swelling was several times the thickness of the jaw with three teeth loosely held and ready to drop out. The tumor was semi-fluctuant, the jaw was destroyed

except for a strip on its lower margin, and an ulceration was present within the mouth. Microscopic examination showed giant-celled sarcoma. The usual surgical procedure would have required resection of at least half the jaw with hopeless mutilation and almost certain recurrence. Radium was placed on the inner aspect of the tumor in the mouth with rapid shrinkage of this part of the tumor. It is interesting to note that with this application, Abbe protected the tongue with lead. Encouraged by the favorable immediate response, Abbe continued treatment by applying the radium between the gum and the lip. This application had to be abandoned soon because of the blistering reaction which occurred. Then the radium was placed into the substance of the tumor through a small incision. This method was repeated frequently, each time in a different position in the tumor. Each time the radium was kept in place for two or three hours. At the end of seven weeks of treatment, during which time, the radium was employed 15 times on different days for a total of 34 hours, there was a severe local reaction characterized by brawny swelling, inflammation, and threatened sloughing. Abbe thought he had overtreated the patient, but the swelling subsided rapidly, the tumor disappeared, new bone formed, the teeth became solid in their beds and the jaw bone was restored to normal contour. After 13 years, the jaw bone was as solid and as perfect in appearance as a normal jaw bone.

It would be interesting to make some sort of dosage estimation for this case in the light of modern dosimetry. If the tube contained 100 milligrams of radium and if the tumor were 4 centimeters in diameter, the dose from the gamma radiation alone would have been about 7000 gamma roentgens, which is above twice the dose necessary to affect a giant cell tumor of bone favorably. The actual dose must have been much higher because of the intense beta ray component which cannot be estimated. On the other hand, the preservation of the teeth intact without decay (which was not reported) indicates a much smaller dose. Probably the dose was very unevenly distributed with "hot spots" in the tumor substance itself where it did not matter. Abbe also mentioned that similar results with giant cell tumors of bone had been demonstrated with roentgen rays by Dr. Pfahler of Philadelphia.

Abbe described this result as the alterative action of electrons reversing the disordered growth of marrow cells. The same type of myeloid tumor in other parts of the body, the upper jaws, humerus,

sternum, sacrum, and tibia, responds in a similar favorable manner and can be cured by radium. Abbe believed that radium is a specific for the giant cell tumor and it was his conviction that every case should be given treatment by radium before any operation and that we can expect many cures.

In comparing radium with surgery in the treatment of epithelial tumors, Abbe remarked that surgeons did not cure this disease by removing or destroying the tumor. Radium, on the other hand, supplies the tumor with a force which works within itself. This force causes the tumor to remove itself, and, if the correct dosage of electrons has been supplied, the growth never comes back. In support of this idea, Abbe mentioned several cases of epithelioma involving the face, scalp behind the ear, and lower eyelid, all of which were successfully treated with radium and were observed to have excellent healing with smooth scars after many years of observation. Abbe was particularly impressed by the result obtained with the tumor of the lower eyelid. The structures of the lower lid were engulfed in the growth beyond identification, more than half the eyelid being involved. The tumor was heaped upon the skin, it mounted up above the edge of the lid and grew inside the lid as on the outside. After a brief radium treatment, shrinkage rapidly ensued. In eight weeks, a normal shaped eyelid was self-restored. The skin was normal in appearance, the edges of the lid were sharp, the mucous membrane was smooth, and the eyelashes grew in again. In nine years of observation, no one could tell on which eyelid the tumor had been.

When the response of the epithelioma of the eyelid to radium is studied, it illustrates a "specific" action of radium that is unlike any other agent. Out of the enormous mass of overgrown cells of the tumor, the original ones which constituted the eyelid and skin were reassembled to a normal structure. The overgrowth of cells retreated or melted away under the action of the radium rays. We have to reckon with a new force in therapeutics from which more may be expected. This alterative action of electrons is a specific and unique action.

Although Abbe was primarily a surgeon, he reported on certain types of tumors for which radium must be credited with a specific cure and which no surgical method could touch. Such a case was a round-celled sarcoma of the skull which was cured by radium. The patient was a man of 45 years. The soft vascular tumor eroded the skull, rested

on the dura, and elevated the skin. Radium tubes were inserted throughout the mass parallel to the dura. The tumor disappeared and did not return after four years. The patient meanwhile maintained perfect health and working power.

Abbe extended the application of radium to almost every field of surgery. He found it effective for the "melting away" of skin recurrences after mastectomy. It was also useful in certain cases of primary cancer of the breast. In one case of cancer of the breast in a 75 year old woman, an ulcerative and bleeding lesion showed rapid healing and shrinking after radium treatment.

Abbe is credited as being the first to use radium in the treatment of cancer of the cervix uteri in 1905. In subsequent years he was able to report several long term survivals with no evidence of disease. Abbe also demonstrated that recurrences in the vaginal vault after hysterectomy could be effectively treated by application of radium.

Abbe found a useful application of radium in operations where complete surgical removal of cancer could not be accomplished. He described one case in illustration in which cancer was incompletely excised because of adherence to the common carotid artery just above the clavicle. At wound closure he therefore placed a strong radium tube against the residual cancer and left it in place for several hours. Subsequently the wound healed and the patient remained well for nine years. On two occasions, Abbe supplemented the excision of carcinomatous masses of the parotid gland with implantation of radium tubes in the operative bed for several hours and in both cases there were no recurrences after four years. Abbe also claimed that the results of hemiglossectomy for cancer of the tongue could be improved by the use of radium at the edges of the excision.

While most of Abbe's use of radium was for cancer, he reported one instance of exophthalmic goiter which he treated by the implantation of a tube of radium into the substance of the greatly enlarged thyroid gland. After eight weeks, the gland was greatly reduced in size and the patient was markedly improved both symptomatically and physically. It is interesting to note that this patient complained of hoarseness after the treatment, which Abbe attributed to enlarged tonsils but which we today would probably attribute to a radiation reaction of the larynx.

Abbe also found radium a useful agent for controlling menorrhagia

due to fibroids. He first used radium for this purpose in 1905 in a case of a large fibroid uterus and he was able to observe the gradual shrinkage of the uterus over a period of years. After experience with 12 cases, Abbe regarded the radium treatment of bleeding fibroids as the procedure of choice in all cases except pedunculated fibroids.

Abbe attempted the use of radium for cancer in inoperable locations, such as tonsils, pharynx, nasopharynx, entire tongue, esophagus, and stomach, and in advanced cancer of the rectum. While no cures were produced in any of these cases, favorable effects were noted such as reduction of masses and improvement in infection and bleeding. In the treatment of cancer of the stomach, Abbe suggested a cross-fire technique whereby the gamma rays of radium could be applied internally through a gastrostomy while external radiation could be obtained either from radium or from an x-ray tube. In inoperable cancer of the rectum, radium was usefully applied to check hemorrhage and relieve pain after a preliminary colostomy.

Abbe recognized that treatments repeated at regular intervals over some period of time gave better results than a single massive treatment. In 1920, he wrote: "If more intensive treatment is necessary, then cumulative or successive attacks are better and an interval of one or two weeks between treatments works out a better result. Thus, successive blows fall upon the disease, sustaining a long corrective action rather than an intense and destructive one." At the time this point of view was written, Henri Coutard in Paris was developing his theory of protraction and fractionation for x-ray therapy, a theory which soon became a universally recognized standard.

During Abbe's career, radium therapy went through a stormy ordeal of enthusiasm and rejection. In this country, we owe a great debt to Abbe for his perserverance, his sustained enthusiasm, and his pioneering spirit. Abbe realized that the whole field of radium therapy was open for progress in both efficient and wider usefulness and for technical improvement in its application. He wrote that: "Great discouragement necessarily follows all pioneer work in new fields, because attempts must be made to test apparently hopeless trails which must be abandoned temporarily, only to be taken up again as new methods prevail. In this line of pursuit, hundreds of advanced cases of cancer have been submitted to test, sometimes mild, sometimes heroic. Discredit and abuse have been undeservedly received. Out of all, however, it is fair to say

that in grave cases much that has been helpful has resulted and in the early cases apparent cure results. More cannot be said to the credit of surgery by cutting methods."

In this statement Abbe summarized the status of radium therapy in the nineteen-twenties. He was the recognized leader in this specialty. After the first world war it was he who was responsible for raising a gift of $100,000 to Madame Curie to continue her research. Madame Curie honored Abbe with the gift of an instrument made by Pierre Curie and used by her. This instrument was later given to the College of Physicians of Philadelphia.

Robert Abbe was a charter member of the American Radium Society and was also the first man to be made an honorary member of this society. At the third annual meeting in 1918, Abbe said he preferred to remain an active member, so the motion to elect him an honorary member was amended to read "active honorary member," a title which truly fitted his character.

Robert Abbe died in 1928, a man of pioneer spirit, of vision and of many great accomplishments. He may rightly be called the founder of radium therapy in America.

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SECTION ON MICROBIOLOGY*

*Abstracts of Papers***

Presented at the Meeting, November 16, 1955 at The New York Academy of Medicine

Histochemistry with Labelled Antibody

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It has been known for some years that antibodies labelled with approximately two molecules of fluorescein per protein molecule can be used as specific fluorochromes for the localization of antigenic material in tissue cells.[1] After applying a labelled antibody solution to a tissue section for long enough to allow the labelled antibody to be bound by the antigen present, then washing off the excess, the fluorescent protein deposit can be visualized under the fluorescence microscope.

Recent modifications in this method by means of layers have allowed the demonstration of antibody in the cells of immune animals. When sections of lymphoid tissue from such animals are exposed to a dilute solution of the specific antigen, antigen is bound by the antibody in the tissue cells. If excess antigen now be washed away, the deposited antigen can then be detected by specific labelled antiserum, and hence the antibody present in the tissue cells visualized. Another use of layers has also been developed. When unlabelled specific antiserum is placed over a tissue section containing antigen, the globulin molecules are deposited from the serum over the sites of antigen localization. After excess unbound serum has been washed away, these globulin deposits can be detected by means of labelled specific anti-globulin serum.[2] Slides illustrating the application of these methods to the detection of polysaccharide and protein antigens injected into animals, antibody in the cells of immune rabbits, and viruses in infected cells, both in susceptible animals and in tissue cultures were shown.

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Mixed Infections with Influenza and Mumps Viruses in the Chick Embryo

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The use of fluorescent antibody in the localization of influenza and mumps viruses following intra-amniotic inoculation into the developing chick embryo[1, 2] has shown that the multiplication of these agents is restricted to the cells lining the amniotic cavity and the epidermal and pharyngeal epithelium. However, while the infection with the influenza virus is characterized by a diffuse type of staining which is first detectable in the nuclei and later in the cytoplasm of the cells, the growth of mumps virus takes place in discrete, multiple foci primarily within the cytoplasm of the cells. To determine whether this difference in localization would permit the viruses to occupy the same cells simultaneously, as has been suggested by the work of Ginsberg, Goebel and Horsfall,[3, 4] these experiments were extended to a study of mixed infections.

The viruses used consisted of the Enders' strains of influenza and mumps viruses passaged serially in eggs. Groups of seven to eight day old embryos were injected into the amniotic sac simultaneously or at intervals with varying amounts of both viruses while the controls received similar injections with either one or the other virus at the appropriate time interval. The eggs were incubated from one to three days and the mortality recorded. Frozen sections were made from the tissues of a representative number of survivors and pairs of consecutive sections were stained with either one or the other homologous labelled antiserum and in some instances with both antisera in succession. The stained preparations were examined under the fluorescence microscope and when necessary photographed.

The results obtained showed that when the viruses were injected simultaneously and the amount of PR8 virus used was large, most of the embryos either died or showed the presence of only the PR8 virus on the third day of incubation irrespective of the size of the mumps inoculum. If, however, the amount of PR8 virus used was very small as compared to mumps virus or if the embryos were examined on the first day of incubation, the amniotic membranes showed varying degrees of involvement with both viruses. In many of the areas, moreover, the viruses appeared to occupy the same cells.

When the mixed infections were produced at intervals, and the influenza virus was given within the first 24 hours after the injection of mumps virus, the results were essentially similar to those of the simultaneous infections. As the interval between the inoculation of the two agents was prolonged to one and two days, however, the infection with mumps virus assumed the ascendancy in direct relation to the size of the inoculum. The staining seen under these conditions showed the presence of varying numbers of cells which appeared to be infected with both viruses, particularly in those areas in which the infection with mumps virus was at an early stage. Finally, by spacing the two injections three days apart or longer, the multiplication of mumps virus became sufficiently advanced, with even the smallest inocula used, to exclude most or all of the PR8 virus injected at this time.

It is, therefore, apparent that the outcome of mixed infections with the viruses of influenza and mumps is governed by the factors of the amounts of each virus used, the interval between injections and the relative rates of growth of the two agents.

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Studies on Primary Atypical Pneumonia

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Some uncertainty has surrounded the identity of the etiological agent of Primary Atypical Pneumonia (PAP), although experimental transmission of the disease to human volunteers[1] suggested that the causative agent is probably a filtrable virus. Current methods for the diagnosis of PAP depend on the clinical picture of the illness, x-ray findings of the lungs and the development of cold agglutinins or streptococcus MG agglutinins in the sera of patients convalescent from the illness.

In 1944, an agent which was transmissible to cotton rats, hamsters, and chick embryos was isolated from PAP patients by Eaton, Meiklejohn and van Herrick.[2] The agent, designated as the Mac strain of PAP virus, has since been propagated in chick embryos for more than 60 serial passages. Suspensions of lung, trachea, and amniotic membranes from infected embryos induce pneumonia in cotton rats by intranasal instillation.

In the present studies of Primary Atypical Pneumonia, the indirect fluorescent staining method as described by Dr. Coons was used. Convalescent sera from human cases of PAP and anti-human globulin fluorescent rabbit sera were employed to detect the localization of viral antigen in infected chick embryo lungs. Furthermore, with known PAP infected chick embryo lung sections, the same procedure can be used to detect and titrate the antibody content of human sera for the serological diagnosis of PAP.

After inoculation of the Mac strain of PAP virus into the amniotic sac of chick embryos, the viral antigens were found to localize in the cytoplasm of bronchial epithelial cells. The infection was distributed primarily in the bronchi near the bifurcation of the trachea and in some of their larger branches. No viral antigens were demonstrated in the heart, the great vessels, or the amniotic membrane of the same infected embryos.

The age of the embryos was important for cultivation of the virus. When ten day old embryos were inoculated into the amniotic sac and incubated at 35°C for seven days, only 30-40 per cent showed viral growth in the lungs. But when 13 day old embryos were inoculated in the same manner and incubated for five days at 35°C, virtually 100 per cent of the inoculated eggs became infected.

Four new strains of PAP virus were isolated by inoculating sputa or lung suspension into the amniotic sac of 13 day old embryos. Three strains were isolated from the sputa of patients during the acute stage of the illness. The fourth strain was isolated from the lung of a patient who died in 1943. This lung was frozen at –70°C since autopsy, and kindly made available to us by Dr. Maxwell Finland. The evidence that they were probably agents from PAP is: 1) These agents react with human convalescent sera but not with acute phase sera from PAP. 2) The growth and localization of the virus in chick embryos are similar to the Mac strain of PAP virus. 3) The agents produce pneumonia in cotton rats when inoculated intranasally, and this pneumonia can be neutralized by human convalescent serum. 4) Antigenically they all cross-react including the Mac strain of virus.

In patients recovered from PAP infection, the antibody responsible for fluorescent staining appeared between the second and the third week of illness and all of them had antibody when the sera were collected three weeks after infection. The rise of antibody as measured by fluorescent staining and by cotton rat neutralization tests was parallel. Among seven patients so far studied, the fluorescent staining antibody has persisted in undiminished titers for three to ten months.

Agglutinins to human 0-type cells (cold

agglutinins) and to the non-hemolytic streptococcus MG frequently develop during the course of PAP infections.[3, 4] The cold agglutinin is unrelated to the PAP fluorescent staining antibody, because absorption of convalescent sera with human 0-type cells in the cold did not affect the fluorescent staining antibody titer. However, absorption of convalescent sera with streptococcus MG organisms did remove or diminish the fluorescent staining antibody titer. Yet rabbit serum with a high streptococcus MG agglutinin titer did not show fluorescent staining on infected chick embryo lung sections, nor did rabbits immunized with PAP virus develop MG agglutinins.

Of 44 PAP patients' sera collected during convalescence in the Boston area, about 70 per cent of them showed fluorescent staining antibody against PAP virus. Of 27 sera collected from characteristic cases of PAP from a private boys' school in New Hampshire, 100 per cent of them developed antibody against the virus. Most of these patients had cold agglutinins when tested. As to the specificity of the serological test for PAP, no cross reactions between influenza A and B infections, psittacosis, Q fever, or APC (Rowe, Huebner et al.) virus and the PAP virus have been encountered.

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The Effect of Colchicine on Antibody Production

NOBUO TANAKA and A. H. COONS

Recent findings have indicated that antibody is first detectable after antigenic stimulation in large undifferentiated cells lying in the medullary areas and around the follicles of the regional lymph nodes. These cells multiply and differentiate, meanwhile their antibody content increases, and by the end of the fourth or fifth day, their descendants form colonies of plasma cells in these regions. This description, which applies to the secondary antibody response, is quite different from the course of events following a first injection, for in this case very few antibody containing cells can be found.[1] Because of the evident dependence of antibody formation, particularly in the secondary response, on the multiplication of differentiating cells, it was thought that the manipulation of antibody response with so-called "mitotic poisons" would shed more light on this process, and accordingly colchicine was chosen as the first compound to be investigated. In 1949 Forman, Seifter and Ehrich[2] investigated the effect of colchicine and other drugs on the development of experimental serum disease in the rabbit, and reported that there was a small drop in the circulating antibody in the animals injected throughout the course of the experiment with full doses of colchicine. Fagræus and Gormsen[3] studied the effect of moderate to full doses of colchicine on antibody production in the rat, and demonstrated that when colchicine was administered on the third day following an injection of antigen, there was a statistically significant fall in the circulating antibody titer.

In our experiments, full doses of colchi-

cine were administered to rabbits at the same time as the second injection of antigen, and a pronounced increase in the amount of antibody present on the eighth day thereafter was demonstrated. The larger the dose of colchicine, the greater was the rise in antibody up to the point where the animals died from the drug. It has also been found that colchicine does not produce this effect when it is administered two days before or two days after the injection of antigen. In control experiments, it was found that colchicine alone does not produce a secondary response, in agreement with Fagræus and Gormsen. We did not investigate in a sufficient number of animals the effect of colchicine injected three days or longer after an injection of antigen, although what data we have are not inconsistent with the report of Fagræus and Gormsen.

No explanation of this effect of colchicine can be offered at the present time, although it is possible that colchicine stimulates the division of the primitive cells from which the antibody synthesizing cells spring. It was originally suggested by Dustin[4] and his collaborators that colchicine stimulated cell division. Later it was shown by Ludford[5] that the greatly increased number of mitotic figures visible during the first day after colchicine administration was due to the arrest of mitosis at the metaphase. More recently, however, Miszurski and Doljanski[6] have presented evidence that colchicine not only arrests mitosis, but also stimulates its occurrence. We have attempted to test this hypothesis by making cell counts of antibody containing cells in the regional lymph nodes of animals with and without colchicine treatment. Although so far our data show more antibody containing cells in colchicine-treated animals, the data are as yet too sparse to yield a statistically significant difference.

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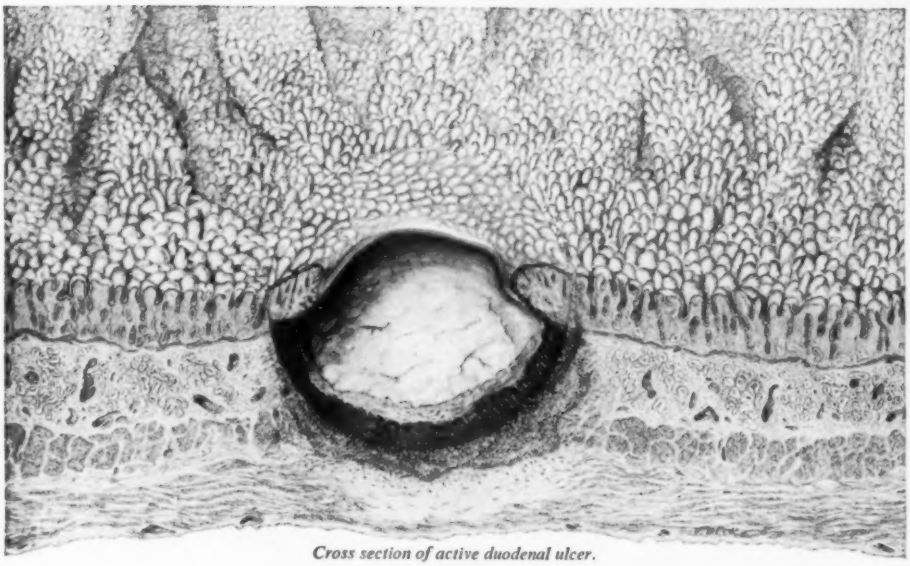
PRO-BANTHĪNE® IN DUODENAL ULCER



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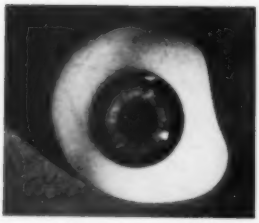

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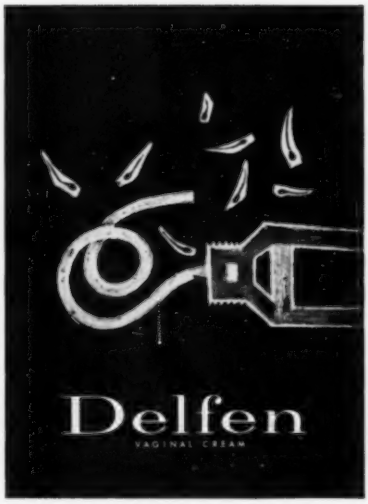

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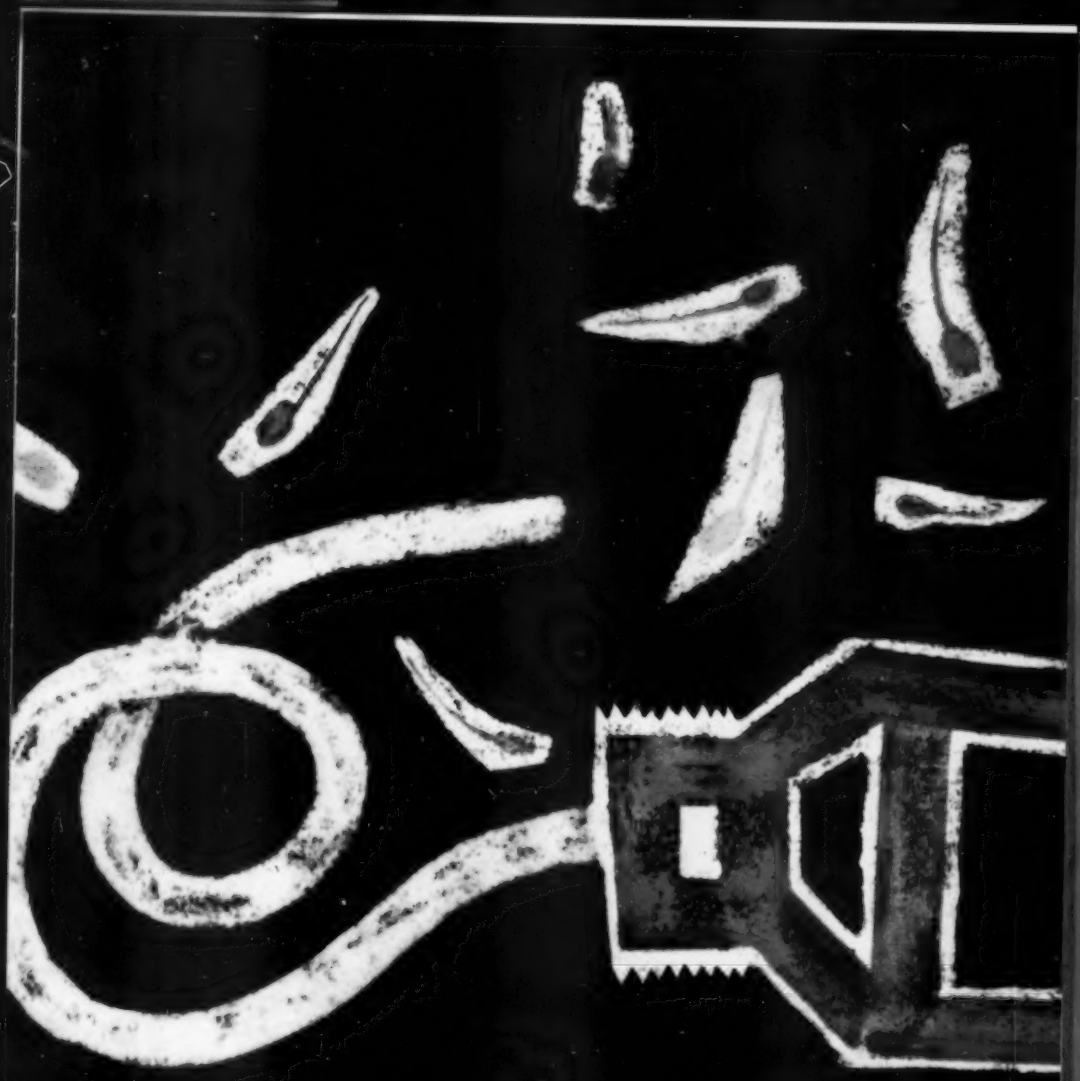

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*Ferrer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:272, 1955

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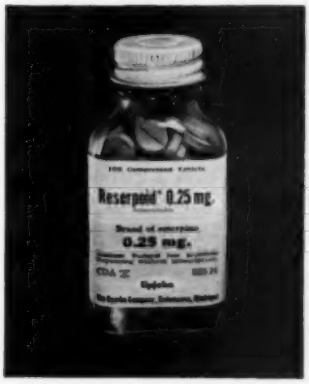

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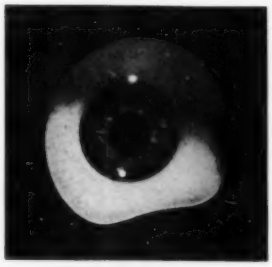

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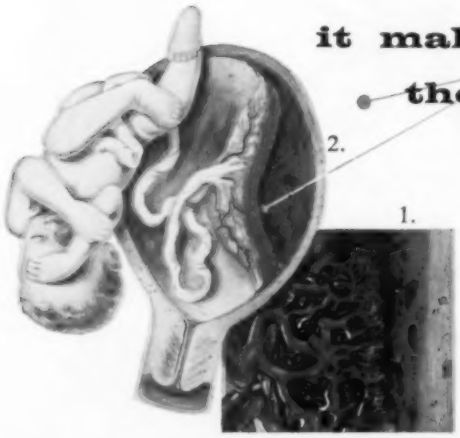

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So often the allergic patient is tired, irritable, depressed—mentally and physically debilitated. Frequently, antihistaminic agents themselves are sedative, adding to this already fatigued and disconsolate state.

Plimasin, because it combines a proved antihistamine with a new, mild psychomotor stimulant, overcomes depression and fatigue while it achieves *potent* antiallergic effects. Its new stimulant component —Ritalin—is totally different from amphetamine: smoother, gentler in action, devoid of pressor effect.

DOSAGE: *One or 2 tablets as required.*

Each Plimasin tablet contains 25 mg. Pyribenzamine® hydrochloride (tripelennamine hydrochloride CIBA) and 5.0 mg. Ritalin® (methyl-phenidylacetate CIBA).

C I B A SUMMIT, N. J.

2/2191M

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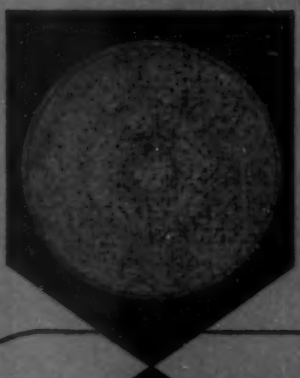
the only broad spectrum antibiotic preparation that...



1 provides the antimicrobial activity of tetracycline

Because it contains Steclin (Squibb Tetracycline), the well tolerated broad spectrum antibiotic, MYSTECLIN is an effective therapeutic agent for many common infections. Most pathogenic bacteria, as well as certain large viruses, certain Rickettsiae, and certain protozoans, are susceptible to Mysteclin.

2 protects the patient against monilial superinfection

Because it contains Mycostatin (Squibb Nystatin), the first safe antifungal antibiotic, MYSTECLIN acts to prevent monilial overgrowth frequently observed during broad spectrum antibiotic therapy. Manifestations of this overgrowth may include some of the diarrhea and anal pruritus associated with antibiotic therapy, as well as vaginal moniliasis and thrush. On occasion, serious and even fatal infections caused by monilia may occur.

Mysteclin

STECLIN-MYCOSTATIN
(Squibb Tetracycline-Nystatin)

Each MYSTECLIN Capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride and 250,000 units Mycostatin (Squibb Nystatin).

Minimum adult dose: 1 capsule q.i.d. *Supply:* Bottles of 12 and 100.

SQUIBB

"MYSTECLIN", "STECLIN" AND "MYCOSTATIN" ® ARE SQUIBB TRADEMARKS

In all your pregnant patients

1. Diet is important

2. . . . *and so is adequate supplementation*

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Mead phosphorus-free prenatal vitamin-mineral capsules

Contain calcium . . . no phosphorus

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Both alike in patient acceptance

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- **SMALL DOSAGE**...just 1 capsule t.i.d.
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